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CASE REPORT

A Case Report of Sustained Cytokine Release Syndrome Due to Glofitamab and Literature Review

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Abstract: Glofitamab is a novel bispecific antibody targeting CD20×CD3, capable of simultaneously targeting CD20 and CD3 to activate T cells and release cytotoxic proteins that kill cancer cells. Cytokine release syndrome (CRS) is one of the most common adverse events observed in clinical trials of glofitamab. In most cases, CRS is mild, transient, and manageable with appropriate treatment. This paper reports a case of persistent CRS in a patient with mantle cell lymphoma following glofitamab treatment and reviews the relevant literature for reference.

Keywords: glofitamab, cytokine release syndrome, cytokines, interleukin-6

Introduction

Glofitamab is the first bispecific antibody globally approved for the treatment of DLBCL and was recently approved in China for relapsed or refractory DLBCL in patients who have received at least second-line systemic therapy.[1] It is a novel bispecific antibody with a 2:1 structure targeting CD20×CD3, enabling the simultaneous targeting of CD20 and CD3, which activates T cells to release cytotoxic proteins against cancer cells. However, the use of glofitamab as an immunotherapy is also associated with cytokine release syndrome (CRS). In clinical trials, CRS was one of the most common adverse events, with an incidence rate of ≥20%, although it was typically mild and manageable within 13 days. This report presents a case of sustained CRS in a patient who experienced persistent elevation of cytokines, particularly interleukin-6, following glofitamab treatment.

Case Information

The patient is a 73-year-old female (160 cm, 73 kg) diagnosed with classic condyloma lymphoma in early November 2018. Immunohistochemistry results revealed CD10(-), CD20(+), CD21 (fdc residual), CD3(-), BCL2(+), BCL6(-), CD5(+), CyclinD1(+), Ki-67 (20–90%+), PAX-5(+), CD23 (fdc residual). Considering the patient's age and condition, VR-CAP+ibrutinib was initially administered. Subsequently, she received multiple lines of treatment, including VR-CAP+ibrutinib, zanubrutinib+venetoclax, and BR+zanubrutinib, but the disease was not effectively controlled. On October 15, 2021, she underwent CD19-CART treatment. The disease relapsed in March 2022, and she entered a double BTKi clinical trial but withdrew due to disease progression on October 8, 2022. On October 9, 2022, she was treated with obinutuzumab combined with salvage chemotherapy, zanubrutinib, pomalidomide, G-Gemox, chidamide,

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and Pola, but remained in a relapsed and refractory state. On September 20, 2023, treatment with linperlisib (80 mg daily) provided partial relief, but the disease progressed again three months later. On February 27, 2024, the patient was admitted to the Department of Hematology, Peking University Third Hospital, for further diagnosis and treatment. She has no history of special medication or drug allergies and denies any family history or other significant medical history.

Diagnostic History and Treatment History

The patient was treated with obinutuzumab combined with glofitamab starting on March 1, 2024. The specific regimen included 1000 mg of obinutuzumab as induction. The infusion process was smooth, and the patient experienced no significant discomfort. On March 10 (d8), the first dose of glofitamab (2.5 mg) was administered with 22.5 mL of normal saline via an intravenous pump at a rate of 2 mL/h. Dexamethasone, acetaminophen, and diphenhydramine were used for pretreatment before the administration of glofitamab. The infusion was well tolerated, but after the infusion, the patient developed scattered wheals and pruritus. Intravenous dexamethasone (2 mg) and calcium gluconate (1 g) were administered immediately as anti-allergic treatment, and the symptoms gradually improved. On March 11 (d9), the patient developed a fever with a peak of 39.2°C, without respiratory symptoms. Blood tests showed WBC 3.77×10^9/L (normal reference value $4.0–10.0\times10^9$/L), ANC 2.84×10^9/L(normal reference value $1.8–7.5\times10^9$/L), NEUT% 75.3% (normal reference value 40–75%), and procalcitonin 0.056 ng/mL (normal reference value < 0.05 ng/mL). Serum cytokines were elevated, with IL-6 at 90 pg/mL (normal reference value <5.4 pg/mL), IL-10 at 56.73 pg/mL (normal reference value <12.9 pg/mL), INF-γ at 56.92 pg/mL (normal reference value <23.1 pg/mL), and TNF-α at 56.42 pg/mL (normal reference value <16.5 pg/mL). Given the patient's medical history, infection was excluded, and CRS grade 1 was diagnosed. The patient received acetaminophen and symptomatic treatment, and the body temperature returned to normal on March 12. On March 12, serum cytokines showed a decrease: IL-6 at 34.72 pg/mL, IL-10 at 20.36 pg/mL, INF-γ at 26.89 pg/mL, and TNF-α at 80.29 pg/mL.

On March 18 (d16), the second dose of glofitamab (10 mg) was administered, with dexamethasone, acetaminophen, and diphenhydramine used for pretreatment. The infusion process was smooth. On March 19, fever reappeared, peaking at 38.8°C, without respiratory symptoms. Blood tests showed WBC 3.80×10^9/L, ANC 2.93×10^9/L, NEUT% 77.1%, procalcitonin 0.059 ng/mL, and ferritin 137 μg/L. Based on the history, CRS grade 1 was considered, and the patient received hormone treatment. The fever subsided by March 20, but serum cytokines gradually increased. On March 23 (d21), serum cytokine levels were as follows: IL-6 1661 pg/mL, IL-10 47 pg/mL, INF-γ 162 pg/mL, and TNF-α 43 pg/mL. After further evaluation, the patient was treated with the IL-6 antibody antagonist tocilizumab on March 26.

On April 3, 2024, the patient had a blood routine check, with IL-6 at 1090.37 pg/mL, which was lower than before. On April 4, the second cycle of glofitamab (30 mg) was administered intravenously without complications. The third cycle was delayed due to thrombocytopenia. As the interval between cycles was prolonged, obinutuzumab (1000 mg) was administered again on April 30. The third cycle of glofitamab (30 mg) was given via intravenous pump on May 7 (d8), with a smooth infusion process, and the patient was discharged on May 9. After discharge, the patient experienced recurrent fever, with a peak temperature of 38.9°C. On May 15, the patient was readmitted for further treatment. Physical examination revealed a temperature of 38.2°C. Repeated blood cultures, pathogenic microorganism tests, NGS examination, and chest CT scans showed no significant abnormalities. Ferritin and other tests were performed, ruling out hemophagocytic syndrome, and the patient's body temperature normalized after hormone therapy. On the night of May 16, the patient's temperature rose again to 39°C, and IL-6 was 203.96 pg/mL. On May 17, the patient was treated with tocilizumab, and her symptoms improved. Given the recurrent fevers, the tumor response was evaluated as SD, and serum cytokines and other inflammatory markers remained elevated in multiple reexaminations (see Table 1 and Figure 1 for details). Based on the patient's laboratory results and medical history, persistent CRS induced by glofitamab was diagnosed.

Discussion and Conclusion

According to the WHO-UMC system for standardized case causality assessment,[2] the association between the occurrence of CRS and glofitamab in this patient was evaluated as "certain". Based on the CRS grading scale,[3] the patient was classified as having grade 1 CRS. PubMed, Embase, Cochrane Library, CNKI, and Wanfang databases were searched from the establishment of each database to September 2024. The search keywords included "Cytokine Release

Table 1 Cytokine Changes in Patients During Glofitamab Treatment (pg/mL)

Date	IL-6 (≤5.4pg/mL)	IL-10 (≤12.9pg/mL)	IFN-γ ≤23.1pg/mL)	TNF-α (≤16.5pg/mL)
Mar.11	90	56.73	56.92	56.42
Mar.12	34.72	20.36	26.89	80.29
Mar.18	13.86	14.53	31.19	0.43
Mar.19	14.65	17.00	15.34	1.00
Mar.20	146.65	19.36	18.75	92.04
Mar.23	1660.99	47.00	161.90	42.97
Apr.3	1090.37	26.48	129.16	120.25
Apr.26	66.74	16.44	34.86	0.96
May.9	94.98	13.80	56.84	4.72
May.16	203.96	15.03	100.68	1.85
May.19	602.45	9.45	28.21	14.39
May.24	6753.46	10.11	180.58	453.65
May.27	803.82	7.55	44.99	166.19
Jun.18	454.01	11.07	69.61	728.41
Jul.10	136.03	3.89	5.14	11.74
Jul.29	107.93	8.28	25.81	63.6

Syndrome", "Glofitamab", and "Cytokine Release Syndrome". Inclusion criteria encompassed all studies on CRS induced by glofitamab, while duplicate publications and animal studies were excluded. After screening, four articles were included in the analysis. Ya-Ting Hsu et al[4] conducted a retrospective real-world study in Taiwan, finding that 34 patients experienced 43 CRS events, including three serious events, which were alleviated by symptomatic treatment. Donald et al[5] reported that 56% of patients developed CRS after the first dose of glofitamab, about 35% after the second dose, and 29% after the third dose, with the incidence decreasing to 2.8% after subsequent doses. Some studies[6,7] have documented fatal CRS events, primarily after the first dose of glofitamab. Elif Birtas Atesoglu et al[7] reported a fatality within two days of CRS onset due to the unavailability of tocilizumab. Consequently, it is recommended that healthcare facilities maintain a stockpile of at least one dose of tocilizumab before the first two cycles of glofitamab.

The glofitamab specification states that the longest duration of CRS ≥ grade 2 was 315.7 hours, approximately 13 days. However, in the above three studies and previous case reports,[8–11] no patient experienced prolonged CRS (≥13 days). In contrast, the laboratory indices and clinical symptoms related to CRS in this patient lasted more than 13 days, including

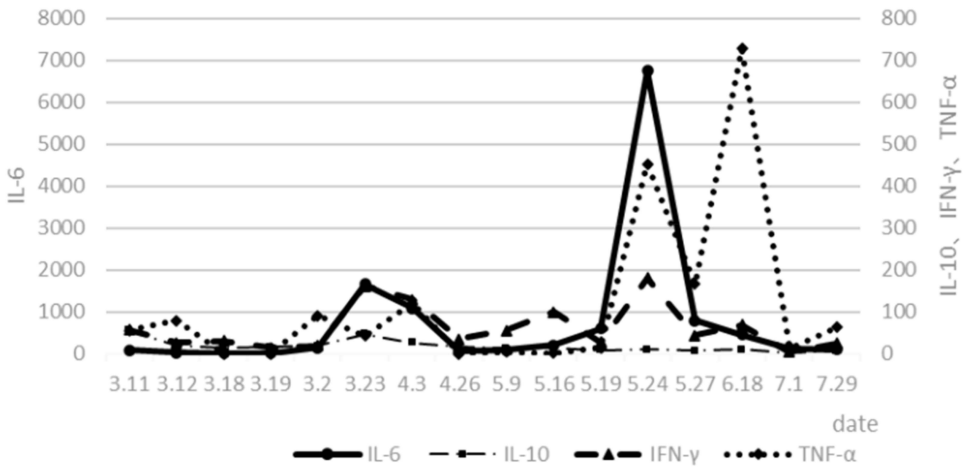

Figure 1 Cytokine changes in patients during glofitamab treatment (pg/mL).

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intermittent fever and persistently elevated interleukin-6, with no normalization of indicators following symptomatic treatment. Therefore, the analysis of this case is both significant and valuable. This case suggests that CRS may be an unmanageable complication in some patients, necessitating a deeper understanding and more effective management strategies. It emphasizes the need for heightened vigilance during treatment with glofitamab and active enhancement of pharmacological monitoring especially during the initial treatment cycle of glofitamab. Once CRS is suspected, early intervention with corticosteroids and/or tocilizumab should be performed according to the severity and CRS grate, with extended follow-up and careful evaluation in case of persistent or recurrent CRS. For patients, the potential risks and benefits of glofitamab therapy, including the possibility of CRS, should be fully understood and the healthcare provider should be informed of any new or worsening symptoms. Patients should also strictly follow follow-up schedules so that health care providers can effectively monitor treatment response and manage adverse events.

Data Sharing Statement

No datasets were generated or analysed during the current study.

Ethical Approval and Informed Consent

This study is in accordance with the ethical standards of our institution and with the 1964 helsinki Declaration and its later amendments or comparable ethical standards. The informed consent form was signed by the patient's daughter as the patient had already passed away. And the patient's daughter consent to publish this case report. The Peking University Third Hospital approval was required to publish the case details.

Consent to Publication

The authors confirm that the work described has not been published before and it is not under consideration for publication elsewhere; and that its publication has been approved by all co-authors, and that its publication has been approved (tacitly or explicitly) by the responsible authorities at the institution where the work is carried out.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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