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CASE REPORT

Secondary Myelodysplastic Syndrome after CD19 CAR T Therapy in Patients with Refractory/Relapsed Lymphoma

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SUMMARY

Background: **Although several chimeric antigen receptor T cells (CAR T) targeting CD19 are curative for patients with relapsed/refractory(R/R) B-cell lymphoma, but the clinical safety and efficacy of this CAR T therapy remain unclear. The risk of secondary malignancies, especially myeloid neoplasms, is of particular concern in the CAR T therapy.**
Methods: **A patient with R/R follicular lymphoma was diagnosed with secondary myelodysplastic syndrome (s-MDS) after CD19 CAR T therapy. We also provided a review of recently published literature concerning the risk of secondary myeloid neoplasms (SMN) following CAR T therapy.**
Results: **The patient had secondary MDS after CD19 CAR T therapy. She received active treatment for nearly one year and then she died.**
Conclusions: **The case illustrated the onset and progression of SMN after CD19 CAR T therapy in patients with R/R B-cell lymphoma and provides useful information of this uncommon later event.**
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KEYWORDS

chimeric antigen receptor T cells (CAR T), R/R follicular lymphoma, cellular immunotherapy, secondary related myelodysplastic syndrome (s-MDS), second cancer

CASE REPORT

The patient was diagnosed with follicular lymphoma in January 2007 at the age of 38, in the Affiliated Jinhua Hospital, Zhejiang University School of Medicine. After six cycles of standard dose R-CHOP chemotherapy, she achieved complete remission (CR). In 2013, the patient's superficial lymph nodes gradually enlarged and were treated with traditional Chinese medicine without improvement. In 2014, chest tightness and shortness of breath occurred, and lymph nodes continued to enlarge. Based on the immunohistochemistry analysis (IHC) analysis of cervical lymph node biopsy, she was diagnosed as B-cell lymphoma. Six cycles of R-DICE treatment were administered, and the disease was relieved. In June 2017, the patient experienced a second recur-

rence and was treated with R-DICE regimen again for 6 cycles and 2 cycles of R. After more than two months of treatment, the patient experienced multiple lymphadenopathy again. Starting from October 2018, the patient received two courses of R-CHOP chemotherapy. However, the patient did not come to the hospital regularly for treatment, and the effect was unsatisfactory. In April 2019, the patient switched to R+Hyper CVAD B treatment, but the effect was still unsatisfactory. Lymph node biopsy was performed again, indicating a transition to DLBCL. In May 2019, R-ECHOP regimen chemotherapy was administered, but the effect was still unsatisfactory. After pre-treatment with FC regimen in July 2019, CD19 CAR T treatment was administered on July 24th, with a total of 1 x 10^6/kg of CD19 CAR T cells transfused. During this period, severe CRS occurred, and subsequent examinations showed sustained remission of the disease. But since April 2021, there has been a progressive decrease in granulocytes, anemia, and thrombocytopenia. October 2021, the bone morphological assessment exhibited the marrow blast percentage of 2%, considering MDS. Bone marrow biopsy showed 3% - 4% primitive cells. Cytogenetics has identified 45, XX, -5, -7, +add (11) (p15), -17, +mar [4]/46, XX [2]; MDS-associated genes revealed the TP53 and GATA2. According to the Revised International Prognostic Scoring System (IPSS-R), she was classified in the very high-risk MDS category. She refused allogeneic hematopoietic stem cell transplantation. Starting from February 2022, she received the hypomethylating agent (HMA) azacytidine (AZA, 75 mg/m^2/day for 7 days every 28 days) for four cycles. In July 2022, the bone morphologic assessment showed 24% primary red and 44% juvenile red, suggesting AML-M6. FCM showed 80.2% primary erythroleukemia, considering pure erythroleukemia. In September 2022, she died from secondary pulmonary infection and gastrointestinal bleeding (Figure 1).

DISCUSSION

The case we have reported is a patient with R/R B cell malignancies who developed SMN after CD19 CAR T therapy. Furthermore, we also reviewed the most recent literature to enhance our understanding of this later complication of CAR T therapy.

CAR T therapy modifies T cells with artificially modified chimeric antigen receptors (CAR) targeting tumor antigens during treatment, combining the high affinity of antigen antibodies with the killing effect of T cells. It can be used for the treatment of acute lymphoblastic leukemia, B-NHL, multiple myeloma, and some solid tumors [1]. This therapy has achieved significant clinical efficacy in recent years, but it also comes with certain risks, including the possibility of causing secondary tumors [2]. Hamilton MP et al. conducted a retrospective analysis of 724 patients who received CAR T therapy at Stanford University between 2016 and 2024, exploring the issue of secondary tumors after treatment. The results showed that the 3-year cumulative incidence rate of the second hematological tumor was 6.5%, reflecting the rarity of the second tumor after CAR T cell therapy. Specifically, a case of secondary T-cell lymphoma leading to death was mentioned in the study, but the authors believe that this may be due to immune suppression caused by CAR T cell therapy rather than directly caused by CAR T cells themselves [3].

At present, the late-stage adverse events of CAR T therapy are not fully understood, especially for second cancers [4]. Barone A et al. analyzed 651 lymphoma patients receiving CD19 CAR T therapy in a prospective observational CART-SIE study in Italy. The research results showed that the incidence of the second primary tumor was 4.3% (28/651), with hematological malignancies being the most common. The author believes that the incidence of secondary primary malignant tumors after CAR T therapy is relatively low and consistent with previous studies. Meanwhile, since all patients have received chemotherapy before CAR T infusion, the late effects of CAR T cells cannot be distinguished from previous cytotoxic treatments [5]. In comparison with primitive MDS, therapy-related myelodysplastic syndrome has always been recognized to induce poorer prognosis and most patients belong to high or very high-risk categories [6]. The occurrence of secondary tumors may be related to the viral vectors used in CAR T therapy. These viral vectors may randomly integrate into the genome of T cells when introducing CAR T cell genes into T cells. If the virus integrates precisely near or inside genes associated with cancer, it may increase the risk of cancer occurrence.

In addition, factors such as the patient's own disease status, other treatments received (such as chemotherapy and radiotherapy), and the specific implementation plan of CAR T therapy may also affect the risk of secondary tumor occurrence [7-9]. This study conducted single-cell precision analysis on a total of over 100,000 pre transfusion CAR T cells from 12 relapsed/refractory B-ALL patients in the world's first clinical trials, revealing the loss of Th2 function in CD19 positive recurrent patients. This discovery provides target genes and key pathways for predicting response and screening patients in clinical practice [10].

The incidence of therapy-related myeloid neoplasms after CAR T treatment ranges from less than 1% to 12.9%. By contrast, up to 10% of NHL patients may develop therapy-related myeloid neoplasms within 10 years after chemotherapy or autologous hematopoietic stem cell transplantation [11]. For patients who may develop a second tumor, close monitoring and timely intervention are necessary. Once signs of a second tumor are detected, the treatment plan should be adjusted immediately, such as considering salvage treatments such as hematopoietic stem cell transplantation (HSCT). In addition, optimizing the implementation plan of CAR T therapy, improving the specificity and persistence of CAR T cells, and enhancing individualized treatment

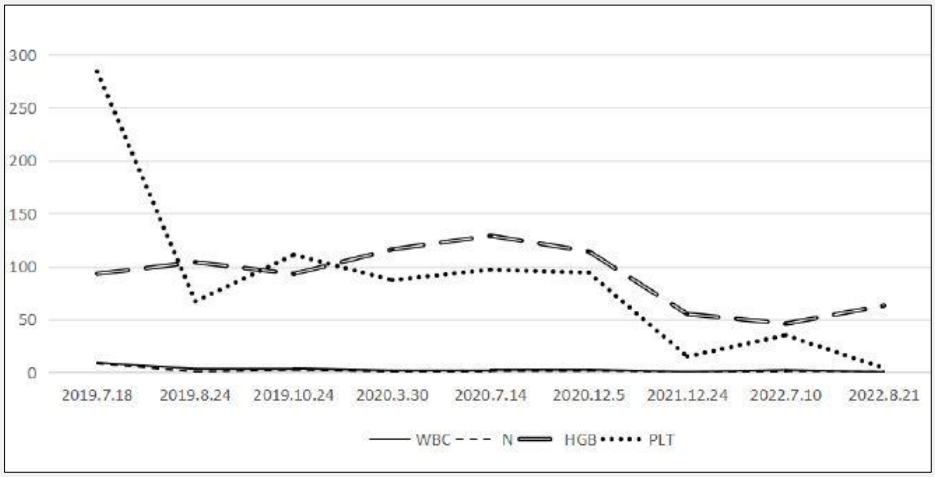

Figure 1. Blood routine.

WBC - white blood cells, N - neutrophils, HGB - hemoglobin, PLT - platelets.

for patients can also help reduce the risk of developing secondary tumors.

The risk of secondary tumors or MDS after CD19 CAR T treatment exists, but this risk is relatively low and can be prevented and managed through various measures. For clinical doctors, it is important to fully understand the patient's disease status and treatment history, develop personalized treatment plans, and closely monitor changes in the patient's condition during the treatment process. Meanwhile, strengthening basic research and clinical trials is also an important way to reduce the risks and improve the efficacy of CAR T therapy.

Informed Consent:

Informed consent was obtained for this case report.

Declaration of Interest:

The authors declare that there is no conflict of interest regarding the publication of this paper.

References:

1. Dana H, Chalbatani GM, Jalali SA, et al. CAR - T cells: Early successes in blood cancer and challenges in solid tumors. Acta Pharm Sin B 2021 May;11(5):1129-47. (PMID: 34094824)

2. Shalabi H, Gust J, Taraseviciute A, et al. Beyond the storm - subacute toxicities and late effects in children receiving CAR T cells. Nat Rev Clin Oncol 2021;18(6):363-78. (PMID: 33495553)

3. Hamilton MP, Sugio T, Noordenbos T, et al. Risk of Second Tumors and T-Cell Lymphoma after CAR T-Cell Therapy. N Engl J Med 2024 Jun 13;390(22):2047-60. (PMID: 38865660)

4. Chakraborty R, Hill BT, Majeed A, Majhail NS. Late effects after chimeric antigen receptor T cell therapy for lymphoid malignancies. Transplant Cell Ther 2021; 27(3):222-9. (PMID: 33928266)

5. Barone A, Chiappella A, Casadei B, et al. Secondary primary malignancies after CD-19 directed CAR-T-cell therapy in lymphomas: A report from the Italian CART-SIE study. Br J Haematol 2024 Jun 15. (PMID: 38877876)

6. Zeidan AM, Al Ali N, Barnard J, et al. Comparison of clinical outcomes and prognostic utility of risk stratification tools in patients with therapy-related vs. de novo myelodysplastic syndromes: a report on behalf of the MDS clinical research consortium. Leukemia 2017;31(6):1391-7. (PMID: 28111463)

7. Gardner R, Wu D, Cherian S, et al. Acquisition of a CD19- negative myeloid phenotype allows immune escape of MLL - rearranged B-ALL from CD19 CAR-T-cell therapy. Blood 2016 May 19;127(20):2406-10. (PMID: 26907630)

8. Perna F, Sadelain M. Myeloid leukemia switch as immune escape from CD19 chimeric antigen receptor (CAR) therapy. Transl Cancer Res 2016 Aug;5(Suppl 2):S221-S225. (PMID: 28824851)

9. Jacoby E, Nguyen SM, Fountaine TJ, et al. CD19 CAR immune pressure induces B-precursor acute lymphoblastic leukaemia lineage switch exposing inherent leukaemic plasticity. Nat Commun 2016 Jul 27;7:12320. (PMID: 27460500)

10. Bai Z, Woodhouse S, Zhao Z, et al. Single-cell antigen-specific landscape of CAR T infusion product identifies determinants of CD19-positive relapse in patients with ALL. Sci Adv 2022 Jun 10;8(23):eabj2820. (PMID: 35675405)

11. Armitage JO, Carbone PP, Connors JM, Levine A, Bennett JM, Kroll S. Treatment-related myelodysplasia and acute leukemia in non-Hodgkin's lymphoma patients. J Clin Oncol 2003;21(5):897-906. (PMID: 12610191)