SAGE Open Medical Case Reports
Volume 13: 1–8

DOI: 10.1177/2050313X241306236
journals.sagepub.com/home/sco
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Combined autologous hematopoietic stem cell transplantation and CD19 CAR T-cell therapy for relapsed/refractory diffuse large B-cell lymphoma with *TP53* mutation: A case report

Ziyi Cai, Dongmei Zou, Qiang Ma, Wanling Sun and Yixian Guo

Abstract

Despite advancements in the treatment of diffuse large B-cell lymphoma, including CAR T-cell therapy, *TP53* mutations remain a significant negative prognostic factor in patients with relapsed/refractory diffuse large B-cell lymphoma. The combination of autologous stem cell transplantation and CAR T-cell therapy may enhance long-term prognosis and reduce adverse effects, including severe cytokine release syndrome. This case report presents a 41-year-old man with relapsed/refractory diffuse large B-cell lymphoma harboring *TP53* mutations who underwent autologous stem cell transplantation combined with CD19 CAR T-cell therapy. Two years posttreatment, the patient remains in sustained complete remission, highlighting the potential efficacy of this combination approach for relapsed/refractory diffuse large B-cell lymphoma with *TP53* mutation.

Keywords

TP53 mutation, CAR T-cell therapy, autologous hematopoietic stem cell transplantation, relapsed/refractory diffuse large B-cell lymphoma

Date received: 18 September 2024; accepted: 25 November 2024

Background

Diffuse large B-cell lymphoma (DLBCL) represents the most prevalent subtype of non-Hodgkin lymphoma, comprising 31%–34% of all cases, with a higher incidence exceeding 40% in Asian populations.[1] Its prevalence increases with age, particularly affecting individuals over 70 years old, constituting approximately 40% of patients.[2,3] *TP53* is a critical tumor suppressor gene, and mutations in *TP53* are adverse prognostic factors in DLBCL patients.[4] Studies have shown that DLBCL patients with *TP53* mutations exhibit poor responses to the standard Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) regimen used as first-line treatment, leading to significantly worse overall survival (OS) outcomes.[5,6] In a study involving 44 DLBCL patients with *TP53* mutations, 27 patients (59.1%) exhibited primary refractory disease following R-CHOP treatment.[7]

The absence of standardized, effective treatments for relapsed/refractory (R/R) DLBCL patients with *TP53* mutations, especially those presenting with additional adverse features such as elevated LDH, multiple extranodal involvement, and large tumor masses, remains a clinical challenge. The advent of CAR-T cell therapy for R/R DLBCL represents a milestone in treatment, killing tumor cells by inducing apoptosis, significantly enhancing the therapeutic landscape for lymphomas, particularly for B-cell lymphomas.[8] However, in clinical practice, patients with large tumor masses or rapidly progressing disease often experience suboptimal outcomes following CAR-T

Department of Hematology, Xuanwu Hospital, Capital Medical University, Beijing, P. R. China

Corresponding Authors:
Wanling Sun, Department of Hematology, Xuanwu Hospital, Capital Medical University, Beijing 100053, P.R. China.
Email: wanlingsun@xwhosp.org

Yixian Guo, Department of Hematology, Xuanwu Hospital, Capital Medical University, Beijing 100053, P.R. China.
Email: guoyixian@xwhosp.org

treatment. The presence of *TP53* mutations continues to be a significant negative prognostic factor in R/R DLBCL patients undergoing CD19 CAR T-cell therapy. One study demonstrated that DLBCL patients with wild-type TP53 had a 1-year OS rate of 76% with CD19 CAR T-cell therapy, while those with *TP53* mutations had a notably lower survival rate of 44%.[9]

Consequently, there is an urgent need to explore novel therapeutic approaches for DLBCL with *TP53* mutations. Several studies have suggested that combining autologous stem cell transplantation (ASCT) with CAR T-cell therapy may enhance long-term prognosis in these patients.[10–13] In patients with TP53 alterations, CAR T-cell therapy alone achieved an optimal objective response rate (ORR) and complete response rate (CRR) of 87.1% and 45.2%, respectively, with an estimated 24-month OS rate of 56.3%. However, when ASCT was integrated into the treatment regimen, the ORR and CRR improved significantly to 92.9% and 82.1%, respectively, and the estimated 24-month OS rate surged to a promising 89.3%. The combination of ASCT and CAR T-cell therapy has been demonstrated in several studies to significantly enhance salvage success rates in patients with R/R DLBCL. Moreover, this combined approach exhibits favorable safety profiles, promotes the proliferation and effector differentiation of CAR-T cells in vivo, and mitigates exhaustion levels of CAR-T cells.[10] Additionally, in one study, this combination therapy demonstrated good safety and mild CRS responses, further underscoring its potential clinical utility.[11] Therefore, ASCT combined with CAR T-cell therapy may be an effective treatment for DLBCL patients with *TP53* mutations, warranting further research and exploration.[14,15] The proposed mechanism of action is as follows: Following a robust conditioning regimen for auto-HSCT, the immunosuppressive tumor microenvironment is diminished, resulting in a significant reduction in tumor burden. Administering CAR-T cell therapy during the period of hematopoietic recovery can effectively eradicate residual disease posttransplant, thereby decreasing the rate of recurrence.[13]

Here, we present a case of an R/R DLBCL patient with a *TP53* mutation who experienced disease progression despite multiple rounds of intensive chemotherapy. This case report presents a patient with R/R DLBCL harboring *TP53* mutations who underwent ASCT combined with CD19 CAR T-cell therapy. Two years posttreatment, the patient remains in sustained complete remission (CR), highlighting the potential efficacy of this combination approach for R/R DLBCL with *TP53* mutation.

Case report

A 41-year-old male patient presented to the hospital, with a history of persistent back pain exceeding 2 months. Magnetic resonance imaging (MRI) of the lumbar spine exhibited abnormal signals in the thoracic 6 vertebra and extramedullary regions (Figure 1), along with multiple enlarged lymph nodes within the mediastinum.

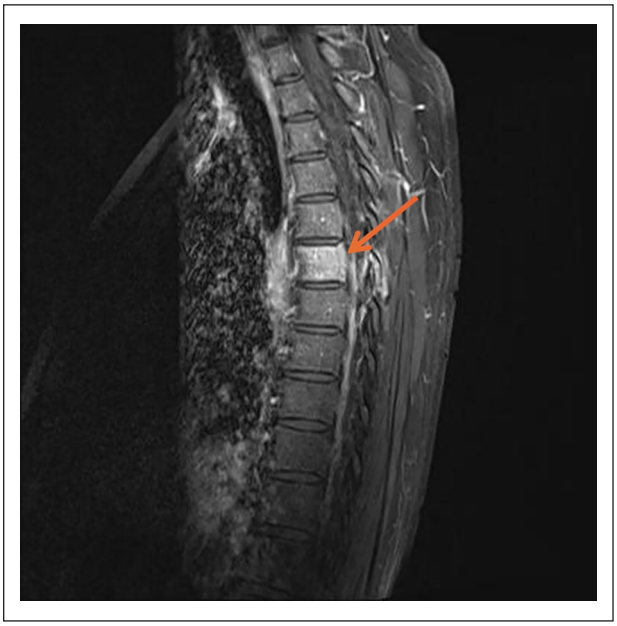

Figure 1. MRI of the lumbar spine exhibited abnormal signals in the thoracic 6 cone.

The patient underwent a percutaneous vertebral needle biopsy. Immunohistochemical results were as follows: TTF-1 (−), CK7 (−), CK20 (−), P63 (partial), P40 (−), CK (−), Vimentin (+), CDX-2 (−), Ki-67 (50%+), CD30 (T lymphocytes+), CD20 (+), CD79a (+), CD5 (a small amount of T lymphocytes+), CD30 (individual+), BCL-6 (partial+), CD10 (−), MUM-1 (part weak+), PAX-1 (+), Cyclin D1 (a few+), BCL-2 (+), P53 (overexpression), c-MYC (40%+), EBV (hybridization in situ) (−), CD138 (a few+), CD38 (−), Kappa (individual+), and Lambda (individual+). the possibility of Non-Germinal Center B-cell-like (non-GCB) DLBCL was considered. Additionally, fluorescence in situ hybridization results were negative for c-MYC.

The patient underwent a bone marrow pathological examination. The results showed that small sheets of proliferative lymphocytes were focally seen in bone and bone marrow tissue (ilium), with single cell morphology and nuclear atypia. Immunohistochemical results were: CD20 (diffuse+), CD79a (diffuse+), CD3 (a few cells+), CD5 (a few cells+), CD30 (−), BCL-6 (−), CD10 (+), MUM-1 (−), PAX-5 (+), Ki-67 (about 70%+), P53 (+), and c-MYC (individual+). Combined with the medical history and the above results, the findings were consistent with non-Hodgkin's lymphoma of B-cell origin, and DLBCL was considered. Bone marrow examination flow cytometry results demonstrated CD19 (+), CD10 (partial +), CD5 (−), CD20 (+), Kappa (−), and Lambda (+), with monoclonal B cells representing 9.5% of the bone marrow. Immunoglobulin gene rearrangement analysis showed positive rearrangement of the heavy chain (IGH).

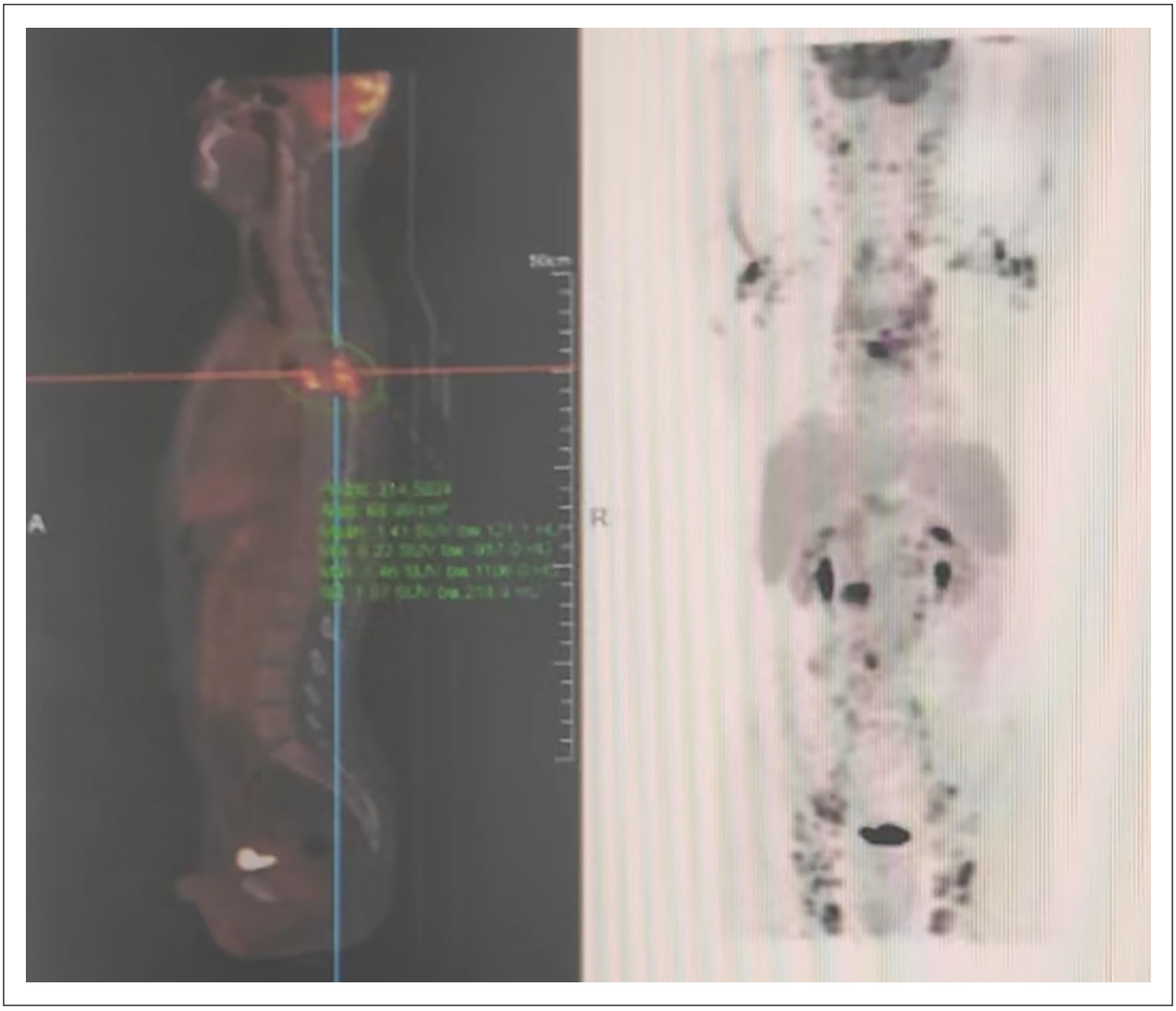

Figure 2. PET-CT shows local bone destruction and increased soft tissue density in the paraspinal region and adjacent spinal canal at the level of the 6th thoracic vertebra, with an SUVmax of 7.46.

Positron Emission Tomography - Computed Tomography (PET-CT) revealed multiple lymphadenopathies in various regions of the body. Notably, an increased uptake was observed in the left gluteal muscle space (SUVmax 7.28). Additionally, local bone destruction and altered soft tissue density were noted in the paraspinal region and adjacent spinal canal at the level of the 6th thoracic vertebra (SUVmax 7.46) (Figure 2). Splenomegaly was also detected (SUVmax 2.03). The SUVmax for liver parenchyma was measured at 1.75, while the SUVmax of the mediastinal blood pool was 1.32.

Next-generation sequencing (NGS) results of the tumor tissue showed that the patient harbored mutations in the *CREBBP, TP53*, and *STAT6* genes (Table 1).

The results of the cerebrospinal fluid examination and enhanced cranial MRI revealed no evidence of secondary central nervous system lymphoma.

In summary, the patient was diagnosed with non-Hodgkin lymphoma (non-GCB DLBCL, DEL) stage IV-A, involving the bone marrow and the 6th thoracic vertebra, accompanied by gene mutations in *CREBBP, TP53*, and *STAT6*. The patient's age-adjusted International Prognostic Index indicated an intermediate-high risk level, and the CNS-IPI suggested an intermediate risk level.

Therapeutic interventions

The patient received multiple lines of chemotherapy and advanced therapies. Initially, the patient was treated with the Rituximab, Dose-Adjusted Etoposide, Prednisone, Vincristine, Cyclophosphamide, and Doxorubicin (R-DA-EPOCH) regimen for four cycles, combined with high-dose methotrexate (HD-MTX) as the first-line treatment. Despite this, the disease

Table 1. The NGS findings of the tumor tissue.

Gene	Transcript ID	Location	Mutation	Variants	Level	VAF (%)
CREBBP	NM_004380	exon27	c.4459C>T	p.His1487Tyr	Level I	49.82
TP53	NM_000546	exon7	c.785_759insTGA	p.Thr253_Ile254insArp	Level I	2.38
TP53	NM_000546	exon8	c.833C>G	p.Pro278Arg	Level I	29.33
TP53	NM_000546	exon7	c.758C>G	p.Thr253Ser	Level II	2.38
STAT6	NM_003153	exon12	c.1256A>G	p.Asp419Gly	Level II	32.10

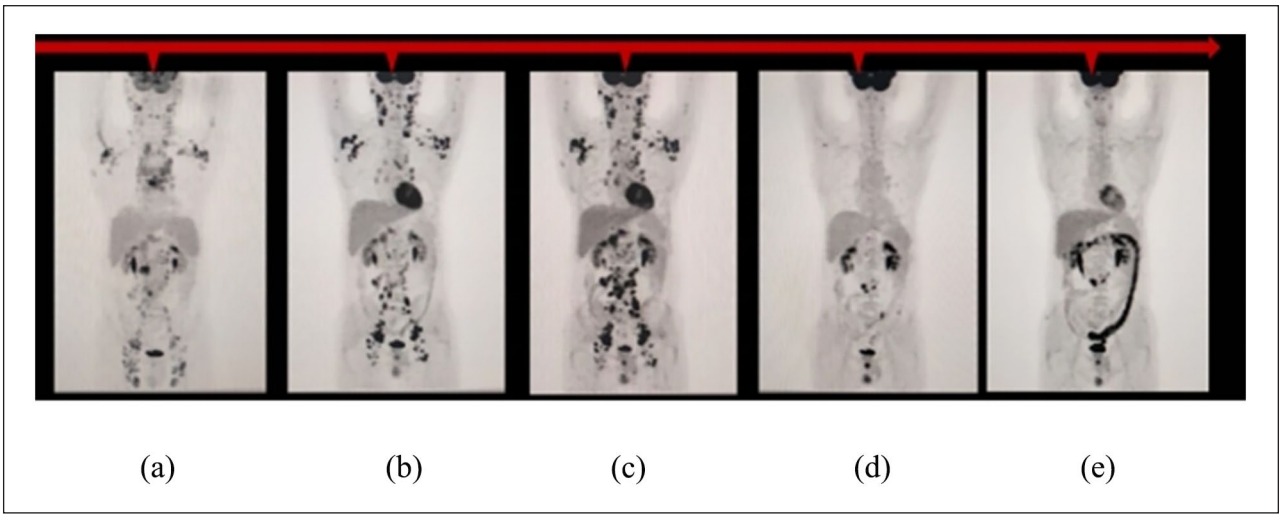

Figure 3. PET-CT imaging throughout the treatment course. (a) Initial imaging before treatment, (b) assessment after first-line treatment with R-DA-EPOCH × 4 + HD-MTX. Outcome: progressive disease (PD), (c) assessment after second-line treatment with R-ICE × 2. Outcome: PD, (d) assessment after third-line treatment with ASCT + CD19 CAR-T. One month later, mesenteric SUVmax: 10.2, bone marrow (BM). Outcome: complete response (CR), and (e) follow-up 3 months after ASCT + CD19 CAR-T. Mesenteric SUVmax: 7.06, BM. Outcome: CR.

progressed, as assessed by the efficacy evaluation indicating progressive disease (PD). Subsequently, the treatment was switched to the R-ICE regimen for two cycles as the second-line therapy, but the disease continued to progress.

Given the lack of response to prior therapies, the patient underwent a ASCT combined with CD19 CAR T-cell therapy (Figure 3) as a third-line treatment. The treatment course was detailed as follows: On D-65, the patient started on R-MA and ibrutinib. Mononuclear cells (5.23×10^8/kg) and CD34+ cells (2.93×10^6/kg) were collected on D-48 and D-47, respectively. Peripheral blood lymphocytes were obtained on D-40. The patient then underwent a BEAM conditioning regimen combined with ibrutinib on D-9. On D0, CD19 CAR-T cells (3.1 ml containing 100×10^6 cells) were infused.

Postinfusion, on D + 4, the patient developed pyrexia. Nonsteroidal anti-inflammatory drugs were used to control the fever, but the patient's temperature remained high 72 h later. By D + 7, the patient experienced Grade I CRS, which was managed with three doses of tocilizumab, but the temperature control was unsatisfactory. On D + 11, the patient developed a generalized rash, and engraftment syndrome was considered. Treatment with 10 mg dexamethasone was initiated, which led to normalization of the patient's temperature and resolution of the rash. Platelet engraftment was observed on D + 12, and neutrophil engraftment on D + 14 (Figure 4).

Follow-up and outcomes

PET-CT and abdominal CT suggested complete response (CR). Fifty days posttreatment, the patient developed bilateral pneumonia, which was resolved with appropriate therapy. CAR-T cells were detectable 254 days postinfusion (Figure 5), and subsequent infections, including COVID-19, were managed effectively. At the last follow-up, 28 months after treatment, the patient was still in CR.

Discussion

This case report highlights a patient with R/R DLBCL and *TP53* mutations who achieved sustained CR following a combination of ASCT and CAR T-cell therapy. The enduring CR in our patient underscores the promising efficacy of this treatment modality, offering valuable insights into managing this challenging condition.

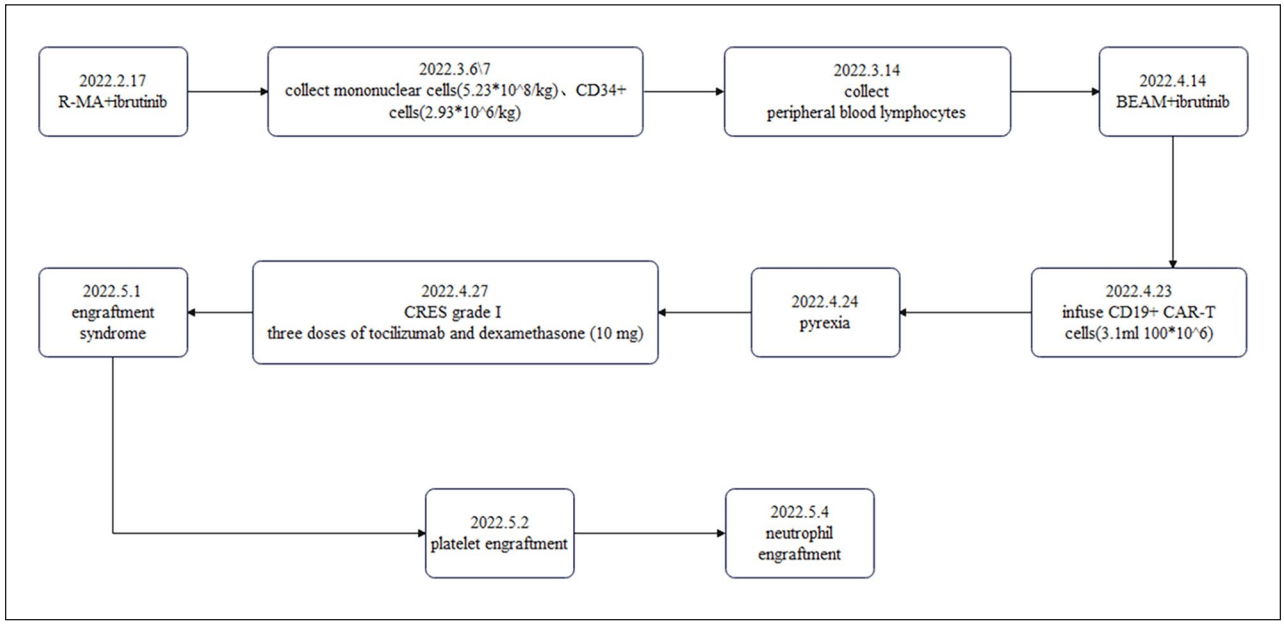

Figure 4. The process flow chart for the third-line treatment with ASCT + CD19 CAR-T.

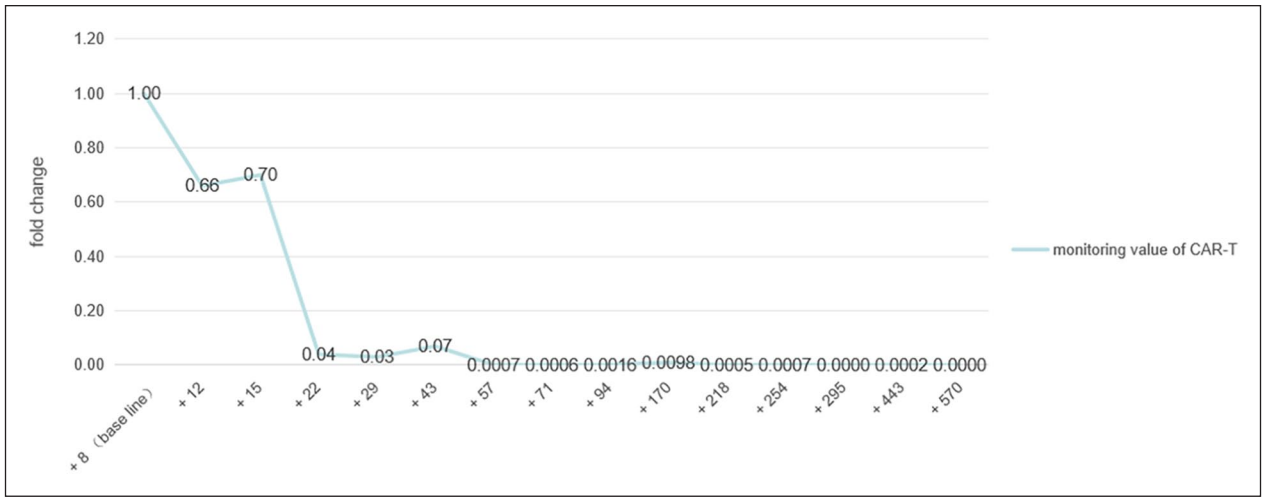

Figure 5. Monitoring value of CAR-T.

NGS played a crucial role in identifying *TP53* mutations, guiding our decision to pursue combination therapy. NGS revealed mutations in the *CREBBP, TP53*, and *STAT6* genes, which informed our decision to pursue the aggressive combination of ASCT and CAR T-cell therapy. The simultaneous occurrence of these three *TP53* mutation sites is exceedingly rare. The *TP53* gene is a major contributor to cancer development and is regarded as the most important tumor suppressor gene. The p53 protein acts as a transcription factor involved in DNA repair, aging, cell cycle control, autophagy, and apoptosis.[16] CREBBP is a key acetyltransferase and transcriptional cofactor that regulates gene expression by modulating the acetylation levels of both histone and nonhistone proteins. CREBBP regulates several essential physiological functions, including apoptosis, proliferation and differentiation, DNA repair, and somatic cell reprogramming.[17] TAT6, a member of the STAT family, is primarily activated by IL-4 and IL-13. In addition to promoting Th2 cell differentiation, it plays a crucial role in the development, differentiation, and class switching of B cells. STAT6 deficiency can lead to impaired immune function, reduced glycolysis, and alterations in B-cell morphology, resulting in a variety of diseases.[18] *TP53* mutations are known prognostic factors associated with poorer outcomes in clinical studies,[4,19,20] even in patients undergoing CD19 CAR T-cell therapy.[6,21,22] The combination of CAR-T cell therapy and ASCT may exert a synergistic effect by augmenting T cell proliferation and

recruitment, while concurrently reducing tumor burden and the incidence of CRS.[23] Consequently, this combined therapeutic approach is anticipated to yield superior clinical outcomes compared to either treatment alone. However, identifying specific *TP53* mutation characteristics that indicate a poor prognosis is crucial. The prognostic impact of *TP53* mutations varies depending on the specific DNA segments affected. For instance, *TP53* mutations in the loop sheet helix and L3 segments correlate with significantly lower survival rates.[24] In this case, three distinct *TP53* mutations were identified at different sites and frequencies. The classification of *TP53* mutations into loss of function (LOF) and non-LOF is a significant contribution, as it has the potential to aid in the identification of patients with *TP53*-associated tumor development disorders. The presence of a higher number of *TP53* mutations suggests an increased likelihood of encountering LOF mutations, which in turn lead to diminished drug reactivity and indicate a poorer prognosis.[25] Personalized analysis, considering mutation type, location, and affected target genes, is essential due to the heterogeneity and functional diversity of *TP53* mutations. Simplifying prognosis solely based on "wild-type" or "mutant" status is inaccurate. Different molecular subtypes of DLBCL, such as those defined by MYD88 and bcl-2, show varying prognostic impacts of *TP53* mutations.[26] The prognostic relevance of *TP53* mutations in Chinese patients requires further exploration.

Preemptive administration of ibrutinib alongside CD19 CAR T-cell therapy is aimed to optimize treatment outcomes and reduce CRS incidence. Statistical analysis supports the efficacy of this combination, with a promising progression-free survival stage of 12.8 months for the ibrutinib group.[27] The TARMAC study assessed the efficacy and safety of time-limited ibrutinib combined with CAR T-cell therapy. Results from this study indicated that 80% of patients achieved CR following treatment.[28] Our patient experienced manageable Grade I CRS without immune effector cell-associated neurotoxicity syndrome (ICANS), suggesting a favorable prognosis possibly attributed to this approach. In managing Grade I cytokine release syndrome (CRS) for our patient, who primarily presented with fever, the approach included fluid replacement and oral acetaminophen. Due to granulocytopenia following high-dose chemotherapy conditioning, we also administered broad-spectrum antibiotics as a part of the treatment. According to CRS management guidelines, if the fever persists for more than 3 days or becomes refractory, tocilizumab (8 mg/kg) may be considered. It is important to note that fever can also occur during cell engraftment and may be confused with CRS symptoms. Careful monitoring for additional signs, such as rashes, liver and kidney function abnormalities, and hypoxemia, is essential. In our patient, a skin rash developed 3 days after the administration of tocilizumab, suggesting the presence of engraftment syndrome. Following the addition of dexamethasone (10 mg), the fever symptoms resolved.

However, combining CAR T-cell therapy with ASCT presents unique challenges, including overlapping toxicities such as conditioning-related toxicity and engraftment syndrome. These complexities necessitate vigilant monitoring and intensive supportive care.[29,30] Diagnosis relies on clinical symptoms and laboratory findings, ensuring stability during this critical period and prompt therapeutic adjustments if necessary. Throughout the treatment continuum following CAR T-cell therapy, comprehensive management is paramount. The incidence of infections underscores the need for proactive monitoring and timely interventions to sustain remission and optimize long-term outcomes.[31] Strategies such as vaccination post-treatment hold promise but require further investigation into safety and efficacy.[32,33] For our patient, long-term follow-up was essential not only to assess disease status but also to address the frequent occurrence of pulmonary infections, including both bacterial and viral infections. This highlights the need for enhanced infection prevention and supportive care for patients undergoing autologous hematopoietic stem cell transplantation combined with CAR-T cell therapy.

The synergistic effects of combining CAR T-cell therapy with ASCT include enhanced T cell proliferation, reduced tumor burden, and potentially mitigated CRS and ICANS incidences.[23] Accordingly, we conducted a combination therapy of ASCT and CAR T-cell therapy to harness their potential synergistic effects, such as enhancing T cell proliferation and recruitment of immune cells to tumor-associated macrophages (TAMs), inhibiting the immunosuppressive components of TAMs, reducing tumor burden, suppressing regulatory cells, and mitigating the incidence of CRS and ICANS following CAR-T cell infusion. This approach aims to enhance the long-term prognosis for R/R DLBCL patients harboring *TP53* mutations.[11] Research suggests that for high-risk patients with refractory relapsed DLBCL, especially those with central nervous system, ovarian, testicular involvement, or significant genetic risk factors, the combination of autologous transplantation and CAR-T therapy may yield better therapeutic outcomes.[13]

Conclusion

This case report demonstrates the efficacy of combining ASCT with CD19 CAR T-cell therapy in treating R/R DLBCL with *TP53* mutations. The synergistic effects of this approach improved the patient's prognosis and minimized adverse effects, suggesting a promising therapeutic option for this R/R DLBCL patient with *TP53* mutations.

Acknowledgements

We would like to thank TOPEDIT for their assistance with language editing and proofreading of this manuscript.

Authors' contributions

YG and WS conceptualized and developed the study. QM performed genetic analyses. DZ, YG, and WS contributed to the patient's diagnosis and treatment. ZC collected and assembled data, analyzed and interpreted data, and wrote the manuscript. All authors revised and provided final approval for the manuscript and were accountable for all aspects of the work.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Undergraduate Scientific Research Training Program of Capital Medical University (XSKY2024).

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient for his anonymized information to be published in this article.

ORCID iD

Ziyi Cai https://orcid.org/0009-0005-9791-0055

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