One Patient Diagnosed With Primary Refractory Diffuse Large B Cell Lymphoma Successfully Salvaged With BCL2 Inhibitor Followed by anti-CD19 CAR-T Suffered From a Secondary Onset of Severely CRS

Yuanfeng Zhang
Qindao University Medical College Affiliated Yantai Yuhuangding Hospital
Shuxiang Sun
Qindao University Medical College Affiliated Yantai Yuhuangding Hospital
Licai An
Qindao University Medical College Affiliated Yantai Yuhuangding Hospital
Yanming Wang
Qindao University Medical College Affiliated Yantai Yuhuangding Hospital
Xiaoxia Chu
Qindao University Medical College Affiliated Yantai Yuhuangding Hospital
Xiaoqian Liu
Qindao University Medical College Affiliated Yantai Yuhuangding Hospital
Yinghui Liu (liuyinghuiyantai@126.com)
Qindao University Medical College Affiliated Yantai Yuhuangding Hospital

Case report

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Abstract

Background

Treatment of relapsed/refractory diffuse large B cell lymphoma (DLBCL) eligible for transplantation is limited by the efficacy of salvage therapy. Chimeric antigen receptor modified T cell (CAR-T) therapy has achieved the highest response rate of salvage therapy for relapsed/refractory aggressive B cell lymphoma. Cytokine release syndrome (CRS) and cytopenia are main side effects of CAR-T therapy.

Case presentation

A 61 years old Chinese male diagnosed as DLBCL was treated with rituximab combined with chemotherapy, unfortunately, he was resistant to first-line chemotherapy and other regimens. Due to high expression of BCL2 protein and amplification of *BCL2* by next sequence generation, BCL2 inhibitor combined with low intensity chemotherapy was given to him as a bridge to anti-19 CAR-T therapy. Although escalation of dose from 100mg per day to 400mg in one week, he had no tumor lysis syndrome and achieved partial response. He suffered persist pancytopenia after CAR T-cells infusion, moreover, a severely secondary CRS on 54th day was observed and responded well to steroid.

Discussion and conclusions

BCL2 inhibitor may have a role in frontline or salvage therapy of DLBCL, especially for those with high BCL2 protein expression, mechanism of which should be still investigated. CAR-T therapy revolutionized the salvage of primary refractory DLBCL, but we should focus on persist cytopenia and severe CRS, and we reported the latest secondary CRS till now.

Background

Although 50–70% newly diagnosed diffuse large B cell lymphoma (DLBCL) could be cured by first-line immunochemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) [1], prognosis of refractory DBCL is dismal, especially for those with primary refractory disease, standard therapy of which is salvage chemotherapy followed by autologous hematopoietic stem cell transplantation (auto-HSCT). However, median overall survival is only 5.1 months for those who had not gone auto-HSCT [2]. Besides conventional chemotherapy, novel drugs including lenalidomide and ibrutinib have been explored in relapsed/refractory DLBCL, demonstrating overall response from 27.5–47% of monotherapy [3–5]. B-cell lymphoma 2 (BCL2) inhibitor monotherapy also have high efficacy in relapsed/refractory indolent lymphoma such as chronic lymphatic leukemia (CLL) and mantle cell lymphoma (MCL) [6], while with limited response in DLBCL [7]. Chimeric antigen receptor modified T cell (CAR-T) therapy has showed the highest efficacy of treating refractory B cell lymphoma with overall response rate (ORR) 82% and complete remission rate (CR) 54% [8, 9]. However, to achieve adequate remission periods that allow time to manufacture and process viable CAR products continues to be an unmet clinical need. Besides, cytokine release syndrome (CRS) and late cytopenia are the main side

effects of CAR-T therapy which always occur in the early and late phase post-infusion respectively. BCL2 inhibitor combined with low intensity chemotherapy bridged for a primary refractory DLBCL followed by CAR-T and a secondary severe CRS more than 50 days after CAR-T therapy was reported firstly in our case.

Case Presentation

This patient was a 61 years old Chinese male, who admitted into hospital for abdominal pain and discomfort in May of 2019. Ultrasound of abdomen showed enlarged lymph nodes and positron emission computed tomography and computed tomography (PET-CT) scan showed diffuse enlargement of lymph nodes (0.5-2.4cm) with high fluorine-18 fluorodeoxyglucose (FDG) intake (maximum standardized uptake value (SUVmax) 4.0-23.7) (Fig. 1A), However, he refused to receive any advanced examination except routinely follow-up. Eventually, he developed severe fatigue and jaundice in November of 2019 and laparoscopic biopsy of his abdominal mass revealed DLBCL which was positive for CD20, BCL2, CD10, MYC, BCL6 with Ki67 proliferation index 70%. Fluorescence in situ hybridization (FISH) detected *BCL6* gene rearrangement of tumor cells while *BCL2* and *MYC* rearrangement were negative. CT showed ground glass like nodules of lungs, pleura thickness, pleural effusion, abdominal mass surrounding head of pancreas and large ascites. His disease status was stage IV with B symptom according to Ann Arbor staging system. Fractioned R-CDOP regimen (rituximab, cyclophosphamide, pegylated liposomal doxorubicin, vincristine, prednisone) was given to him and his symptom and abdominal mass resolved quickly. Unfortunately, his mass appeared again before the second cycle, then second and third R-CDOP were given to him. Based on Lugano 2014 criteria, interim clinical response after three cycles was stable disease. Next generation sequence of his peripheral blood showed *BCL2* amplification and *TP53* mutation. Second line regimen R^2 + GDP (rituximab, lenalidomide, gemcitabine, dexamethasone, and cisplatin) failed to improve his disease status and third line R^2 + ibrutinib + reduced intensity ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin) transiently relieve his abdomen discomfort but jaundice appeared again after another course of R^2 + ibrutinib without chemotherapy due to cytopenia (Fig. 1B). Since high expression of BCL2 protein and *BCL2* amplification of his tumor cells, we determined to treat him with BCL2 inhibitor plus low intensity chemotherapy including vindesine and dexamethasone, with BCL2 inhibitor escalation from 100mg to 400mg in one week quickly. Surprisingly, ten days after treatment, no tumor lysis syndrome (TLS) was observed and physical examination found reduction of abdominal mass. Three weeks after BCL2 inhibitor therapy, PET-CT scan showed obvious reduction of FDG intake among these lesions (SUV_{max} 3.7) (Fig. 1C) with partial remission. To prolong duration of response, autologous peripheral T cells were apheresis collected and transduced with an apoptosis-inducible, safety-engineered lentivector CAR containing four intracellular signaling domains: CD19-scFv//CD28/CD137/CD27/CD3ζ-iCasp9[10]. Lymphodepleting regimen consist of fludarabine 30mg/m2 and cyclophosphamide 500mg/m^2 for 3 days was given before CAR T-cell infusion. The dose of CAR T-cells were 2.4×10^6/kg. He suffered from fever on day 5 and 6, not exceeding 38.2°C, and after excluding infection, grade 1 CRS was diagnosed. Ten days after infusion, physical examination showed disappearance of his abdominal mass, however, delayed pancytopenia appeared

and lasted for more than two months (Fig. 2). Moreover, on 54th day of infusion, he complaint of high fever and short of breath, with low blood pressure and high C reactive protein (CRP). Ultrasound of his heart showed ejection fraction 66%. However, his symptom didn't resolve by antibiotic therapy. On 57th day, his ferritin increased from 2340ng/ml on 55th day to 55577ng/ml with interleukin-6 (IL-6) from 277.8 pg/ml to 903 pg/ml, then dexamethasone 10mg q6h was given for a secondary severe CRS. 0n 58th day, his B-type natriuretic peptide (BNP) increased to more than 5000 pg/ml with cardiac troponin I (cTNI) 2499 pg/ml revealing acute cardiac injury (Fig. 3). However, he responded well to steroid, including rapid control of pyrexia, return to normal level of cardiac function and cardiac enzyme, which supported diagnosis of a secondary CRS. PET-CT of the third month demonstrated partial remission with obvious reduction of abdominal mass (Fig. 1D) and he is still in follow-up now.

Discussion

BCL2 protein family are associate with cell apoptosis [11], inhibitor of which have revealed high efficacy in newly diagnosed or relapsed CLL an MCL, alone or combined with other drugs [6, 12, 13]. Double hit lymphoma is defined as rearrangement both of *MYC* and *BCL2* or *BCL6* detected by FISH. Double expressor lymphoma is high expression of BCL2 and MYC protein by immunohistochemistry, cutoff of which is 50% and 40% respectively. There are several studies reporting the outcomes of BCL2 inhibitor combined chemotherapy as first or salvage therapy for refractory or relapse DLBCL [14–16]. One prospective phase II study found trend was observed for improved investigator-assessed PFS for venetoclax plus R-CHOP as a front-line therapy in the BCL2 IHC-positive subgroups (HR = 0.55, 95% CI, 0.34–0.89), compared with R-CHOP [16]. However, ORR of BCL2 inhibitor monotherapy for relapsed/refractory DLBCL is only 15%-18% without details of BCL2 protein expression [6, 7]. Our patient relapsed with *TP53* mutation and amplification of *BCL2*. *TP53* mutation is related with poor prognosis of DLBCL [17] while amplification of *BCL2* is in accordance with its high expression on immunochemistry [18]. Surprising, he responded well to rapid escalation of this drug without TLS which indicated different mechanisms of drug function from CLL and MCL.

The incidence of CRS followed by CAR-T therapy for lymphoma is high, ranging from 37–93%, onset from 1 to 17 days post-infusion with a median duration of 7–8 days [8, 19, 20], clinical manifestations including pyrexia, myalgias, fatigue, hypotension requiring vasopressors, respiratory failure, coagulopathy and multiorgan system failure. Late cytopenia is also one common side effect of CAR-T therapy, possibly due to cytokines released [21, 22]. Our patient suffered from persist pancytopenia shortly after infusion. Moreover, he developed high fever on 54th day with a peak of inflammatory cytokines including IL-6, ferritin and CRP, followed by acute cardiac and liver injury controlled immediately by steroid. His response to steroid confirmed a secondary CRS. We noticed a second expansion of his CAR T-cells in the peripheral blood (Fig. 4) and mild recovery of his white blood cell at the same time. Recently, a new model of CRS in B non-Hodgkin lymphoma was introduced, which consisted of four stages, CAR T-cell local expansion stage (stage 1); CAR T-cell overflow and inflammatory cytokine surge stage (stage 2); CAR T-cell redistribution and organ damage stage (stage 3) and recovery stage (stage 4). They thought for patients with incomplete bone marrow (BM) recovery, chronic CRS can ignite secondary acute CRS under certain

conditions [23]. Our patient had sigh of systemic CRS except mild fever after infusion which may be due to rapid and persist bone marrow suppression (BMS) without sufficient monocytes in blood or bone marrow stimulated by CAR-T cells to secrete cytokines such as IL-6 in stage 2 [24, 25]. However, his tumor continuously regressed indicating silent effect of CAR T-cells. His secondary severe CRS may be related with recovery of leukocyte (Fig. 2A), which were activated by CAR T-cells and then damaged the target organs (stage 3). In this model, the author thought tumor burden and the level of BMS were determinants of CRS, but our case indicated that BMS may be a double-edged sword.

Conclusions

Firstly, BCL2 inhibitor may have a role in frontline or salvage therapy of DLBCL or as a bridge for CAR-T therapy, especially for those with high BCL2 protein expression, mechanism of which should be still investigated. Secondly, CAR-T therapy revolutionized the salvage of primary refractory DLBCL, but we should focus on CRS and cytopenia. Finally, our case was the latest severe secondary CRS ever reported.

Abbreviations

DLBCL: diffuse large B cell lymphoma; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; auto-HSCT: autologous hematopoietic stem cell transplantation; CLL: chronic lymphatic leukemia; MCL: mantle cell lymphoma; CAR-T: chimeric antigen receptor modified T cell; ORR: overall response rate; CR: complete remission; CRS: cytokine release syndrome; PET-CT: positron emission tomography and computed tomography; FDG: fluorine-18 fluorodeoxyglucose; SUV_{max}: maximum standardized uptake value; R-CDOP: rituximab, cyclophosphamide, pegylated liposomal doxorubicin, vincristine, prednisone; GDP: gemcitabine, dexamethasone, and cisplatin; ESHAP: etoposide, methylprednisolone, cytarabine, and cisplatin; TLS: tumor lysis syndrome; CRP: C reactive protein; IL-6: interleukin-6; BNP: B-type natriuretic peptide; cTNI: cardiac troponin I; BM: bone marrow; BMS: bone marrow suppression.

Declarations

Ethics approval and consent to participate

The research protocol referenced in this manuscript abided by Declaration of Helsinki and has been approved by the Ethics Committee of the Affiliated Yantai Yuhuangding Hospital of Qingdao University.

The patient provided written informed consent.

Consent for publication

Consent for publication of details and images about disease has been obtained from this patient.

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

YFZ: analyzed and interpreted the patient data, drafted the manuscript. SXS, LCA, YMW: analyzed and interpreted the patient data. XXC, QXL and YHL: design the treatment plan, reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Figures

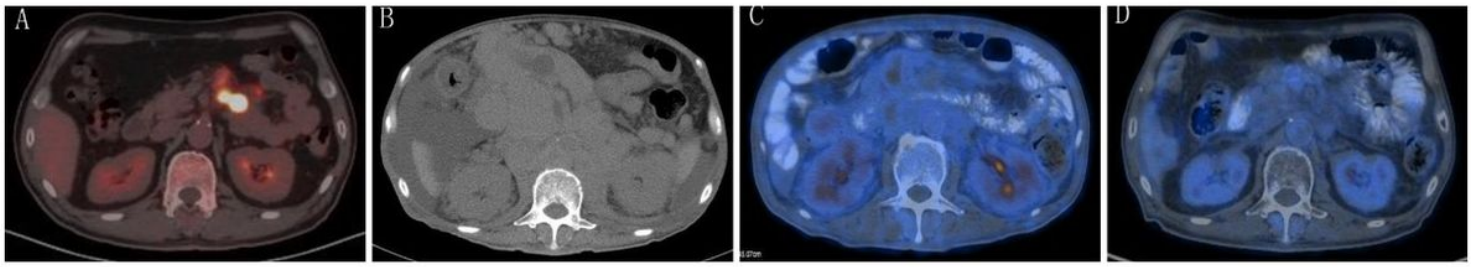

Figure 1

Imaging of this patient A: PET-CT scan showed limited enlarged lymph nodes with high FDG intake in the abdomen at the beginning. B: Fused large mass in the abdomen was found on the CT scan before BCL2 inhibitor therapy. C: Obvious reduction of the mass after salvage with BCL2 inhibitor (3 weeks). D: PET-CT of the 3rd month post-infusion showed disappearance of mass and SUVmax 4.8 of residual lymph nodes compared with liver 3.5 defined as partial remission.

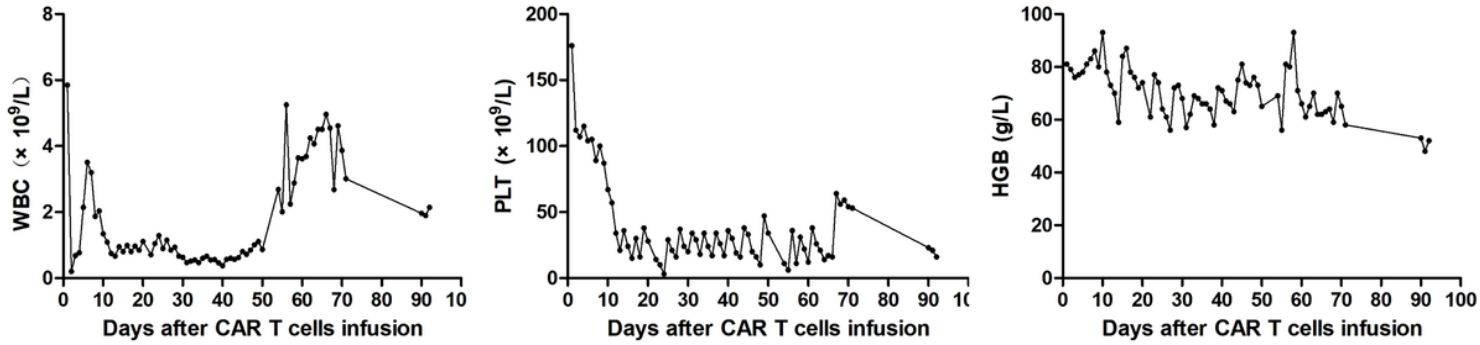

Figure 2

Pancytopenia after CAR-T therapy

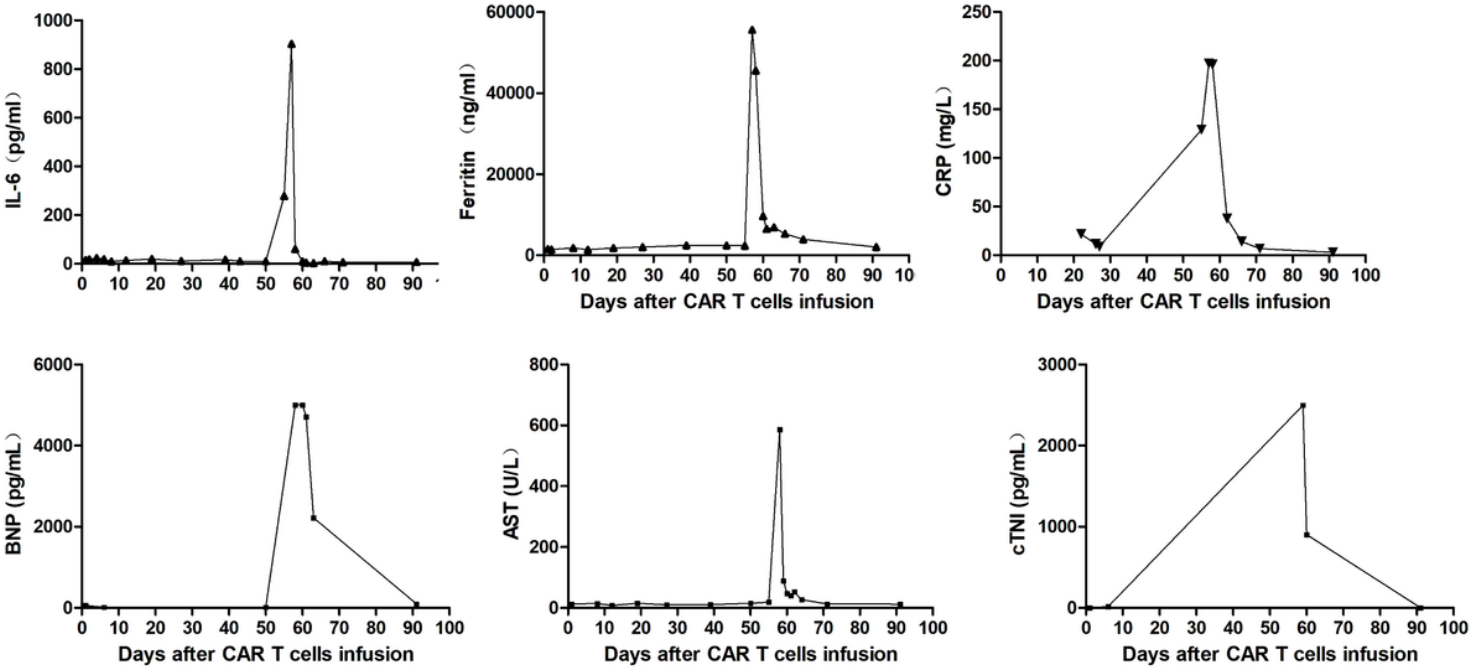

Figure 3

Peak of cytokines and organ specific biomarkers due to a severely secondary CRS

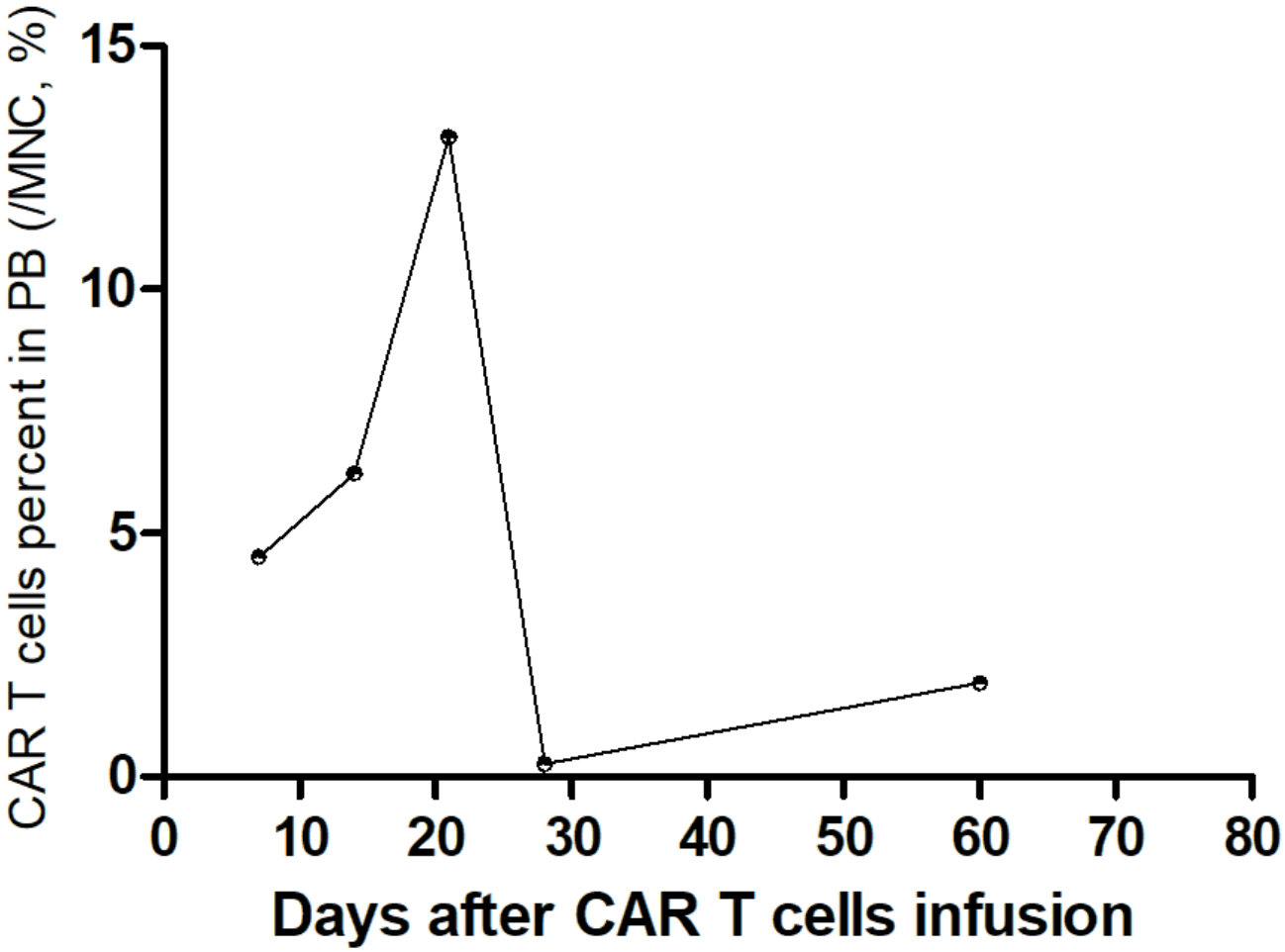

Figure 4

Dynamics of CAR T-cells in peripheral blood