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Refractory diffuse large B lymphoma treated with chimeric antigen receptor T combined with programmed cell-death protein-1 inhibitor: A case report

Refractory diffuse large B lymphoma treated with CAR T combined with PD-1 inhibitor

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Abstract

BACKGROUND

Diffuse large B-cell lymphoma (DLBCL) is a common aggressive non-Hodgkin's lymphoma (NHL), accounting for 30-40% of adult NHL. Primary testicular lymphoma is an uncommon extranodal disease representing approximately 1%-2% of lymphoma. Approximately 40–30% of patients are refractory to frontline therapy or relapse after complete remission. Refractory DLBCL responds poorly to other lines of chemotherapy, and experiences short-term survival[4].

CASE SUMMARY

We present a 41-year-old male patient who was diagnosed with primary testicular diffuse large B-cell lymphoma (PT-DLBCL).Further disease progression was observed after multiline chemotherapy. Chimeric antigen receptor T cells (CAR-T) therapy salvaged the patient; Unfortunately, a new mass was observed in the right adrenal area after six months.The patient was administered programmed cell-death protein-1(PD-1) inhibitor therapy and maintained progression-free survival at more than 17 mo of follow-up.

CONCLUSION

Our findings support the potential benefit of CAR-T combined with PD-1 inhibitor therapies in this type of relapsed and refractory primary testicular diffuse large B lymphoma(PT-DLBCL).

Key Words: Refractory diffuse large B-cell lymphoma;PD-1 inhibitor; CAR-T; Case report

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Core Tip: Primary testicular diffuse large B-cell lymphoma (PT-DLBL) is an uncommon extranodal disease of lymphomas. Refractory diffuse large B-cell lymphoma(DLBCL) responds poorly to other lines of chemotherapy, and is associated with short-term survival. Herein, we report one rare case of chimeric antigen receptor-T（CAR-T） combined with programmed cell-death protein-1(PD-1) inhibitor to treat refractory DLBCL in a 41-year-old male. Our findings support the potential benefit of CAR-T combined with PD-1 inhibitor therapies in this type of refractory DLBCL.

INTRODUCTION

Primary testicular lymphoma (PTL) is a rare lymphoma with a poor prognosis and poor response to conventional chemotherapy. PLT represents approximately 1%-2% of lymphomas[2]. Approximately 40–30% of patients are refractory to frontline therapy or relapse after complete remission[3].Chimeric antigen receptor T cells(CAR-T) have a significant effect on recurrent refractory lymphoma, with good effects on most clinical manifestations in the early stage but for a short duration. The use of programmed cell-death protein-1(PD-1) inhibitors improves tumor immunity in the microenvironment and the immune efficacy of CAR-T cells. It is unclear whether it has unique clinical and biological characteristics, and the therapeutic mechanism needs further study. Therefore, we report a case of primary testicular diffuse large B-cell lymphoma treated with a PD-1 inhibitor after CAR-T therapy. The clinicopathological characteristics and the mechanism of CRT-T combined with PD-1 inhibitor therapy are discussed based on relevant literature, which helps to improve clinical understanding.

CASE PRESENTATION

Chief complaints

A 41-year-old man with an 8-month history of right testicular enlargement.

History of present illness

On June 29th, 2018, he underwent right orchiectomy and right inguinal lymph node biopsy. He had no history of trauma, fever, or other complaints. Physical examination showed unilateral enlargement of the right testicle without any superficial lymph node enlargement. The patient received a right orchidectomy. The histopathological diagnosis of diffuse large B-cell lymphoma (non-GCB) was rendered. Hematoxylin and eosin-stained sections showed diffuse proliferation of medium-sized round cells. Immunohistochemistry (IHC) revealed that the neoplastic cells expressed CD19, CD20, CD79a, and CD21 and were negative for CD3, CD5, CD10, CyclinD1, and ALK. Ki-67 was positive in 80% of tumor cells. BCL-2 was positive in 80% of tumor cells. BCL-6 was partially positive. C-myc was positive in 60% of tumor cells (Figure 1). The patient was diagnosed with diffuse large B-cell lymphoma (non-GCB) IV. On July 13th, 2018, four cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) were given at the local hospital. A follow-up abdominal CT scan showed that the lymph nodes continued to enlarge beside the right iliac vessels. On November 13, 2018, a PET-CT scan showed multiple enlarged lymph nodes (4.3×2.7 cm) beside the right iliac vessels. Two cycles of R2-HyperCVADA (lenalidomide, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) were given. A treatment intensification strategy was applied, and second-Line R-DHAP (rituximab, dexamethasone, cytarabine, and cisplatin) was administered. On July 15, 2019, a follow-up PET-CT scan showed that, in addition to the right iliac vessels, the lymph nodes continued to enlarge (4.3 cm×3.8 cm).

History of past illness

His past medical history included diabetes and cervical spondylosis.

Personal and family history

No personal or family history was available.

Physical examination

Physical examination showed no palpable lymph nodes, organomegaly, or cutaneous lesions.

Laboratory examinations

The peripheral blood and biochemical parameters (liver and renal function and serum lactate dehydrogenase level) were within normal limits. Bone marrow (BM) smear and biopsy did not show evidence of involvement by lymphoma cells.

Imaging examinations

On November 13, 2018, a PET-CT scan showed multiple enlarged lymph nodes (4.3×2.7 cm) beside the right iliac vessels and a high standard uptake value (SUV) with a Deauville score of 18.4 (Figure 2 A-B).

On July 15, 2019, a follow-up PET-CT scan showed that, in addition to the right iliac vessels, the lymph nodes continued to enlarge (4.3×3.8 cm). The standard uptake value (SUV) was high, with a Deauville score of 17. New viable lesions were found in the right adrenal gland, right seminal vesicle gland and surrounding prostate gland, and right groin (Figure 3 A-B).

FINAL DIAGNOSIS

Based on the above findings, the final diagnosis was made as refractory primary testicular diffuse large B-cell lymphoma (PT-DLBCL), stage IVB.

TREATMENT

On July 24th, 2019, the patient was transferred to the First Affiliated Hospital of Zhejiang University and treated with CAR-T cells at a dose of 5×106/kg. Lymph node size significantly reduced after CAR-T therapy. Unfortunately, in June 2020, an abdominal CT scan showed a new mass in the right adrenal area with a size of approximately 2.8×1.3 cm. On June 11, 2020, PD-1 blockade therapy with sintilimab (100 mg once every 3 wk) commenced. The mass shrank soon after the sintilimab injection.

OUTCOME AND FOLLOW-UP

A year later, a PET-CT scan showed no viable lesions(Figure 3). CAR copies were 9574.28 cells/L on July 6, 2021. He has maintained complete remission until now.

DISCUSSION

Primary testicular lymphoma (PTL) is a hematological malignancy with a low clinical incidence of 0.26 cases per 100,000 person-years[5]. PTL accounts for approximately 1-7% of testicular malignancies and approximately 1-2% of all lymphomas[2]. PTL is the most common lymphoma among males over 60 years of age. The most common histopathological diffuse large B-cell lymphoma in PTL, which accounts for approximately 80-90% of all PTLs, is called primary testicular diffuse large B-cell lymphoma (PT-DLBCL) [6]. The primary clinical manifestation of PT-DLBCL is a painless enlargement of testicular tissue with occasional fever and night sweats, and weight loss. PT-DLBCL is highly aggressive and has a poor prognosis, with a median survival of 1-2 years, especially in patients with late clinical stages (stages III-IV), usually presenting with systemic multivisceral involvement within 2 years[7].

The clinical characteristics of PT-DLBCL are low incidence, high aggressiveness and complex treatment, which may explain the lack of a standard treatment at present. The recommended conventional treatment is chemotherapy after orchiectomy, which cures 60% to 70% of patients[8]. However, a small number of patients have a poor response to treatment, with frequent recurrence and poor prognosis. Prognostic factors regarding testicular lymphoma have been suggested in several large retrospective reports[9]. In 2003, the International Extranodal Lymphoma Study Group (IELSG) suggested that advanced age, advanced stage, a high IPI score, elevated lactate dehydrogenase, and the absence of surgery or radiation therapy were significantly associated with poor prognosis[10]. In 2011, Battista *et al* found that first-line treatment with R-CHOP, IT-MTX and testicular radiotherapy could improve the prognosis, while non-GCB cell phenotypes had a worse prognosis than GCB cell phenotypes[11]. In 2018, Thomas A *et al*

found that patients with B symptoms, intranodal lymphoma, and concurrent MYC, BCL-2, or BCL-6 rearrangements ("double hit" or "triple hit") generally have a poor prognosis[12]. In this patient, advanced age, a high IPI score, elevated lactate dehydrogenase, and the fact that lymphoma persisted after multiple first-line chemotherapies suggested a poor prognosis. Therefore, second-line treatment can be selected according to 2021 NCNN guidelines [13], and CAR-T treatment can be given in combination with therapy depending on the patient's family's economic situation.

In recent years, there has been an increase in tumor immunotherapy use, especially chimeric antigen receptor T cells (CAR-T), which have been widely used to treat hematological tumors. CAR-T has an efficiency of approximately 80% and an OS rate of 52% at 18 mo in refractory large B-cell lymphoma [14]. The principle of CAR-T therapy is to genetically modify T lymphocytes to express a specific receptor (CAR) to target and bind specific antigens so that T cells can specifically recognize tumor cells and kill tumors[15]. In contrast to T cells under normal conditions, CAR-T cell recognition bypasses the antigen presentation phase. It thus is not restricted by MHC molecules, preventing cancer cells from escaping immune system recognition due to the downregulation of tumor MHC molecules[16]. CAR-T cell therapy can significantly improve the remission rate of relapsed refractory lymphomas, but some patients fail to achieve the desired outcome.

In the disease state, tumor cells upregulate the expression of immune checkpoints by immunosuppressive cells and bind to corresponding sites on T cells. This inhibits the killing activity of T cells and helps the cancer cells evade immune monitoring and attack from the body, thereby promoting their survival[17]. Programmed death molecule 1 (PD-1) is an immune checkpoint protein expressed on T cells. PD-1 binding to the receptor induces phosphorylation, which inhibits downstream activation of the T-cell receptor, limits T-cell proliferation activity and reduces its killing effect on tumor cells. In addition, the immunosuppressive effect of PD-1 Limits T cells. It affects the function of other lymphocyte subsets, such as promoting the proliferation and immunosuppression of regulatory T cells (Tregs) and inhibiting the activity of B cells

and natural killer cells. Therefore, blocking the PD-1/PD-L1 pathway increases the number of T cells and enhances cytokine secretion and reduces Treg cells and bone marrow-derived suppressor cells (MDSCs) to alter the inhibitory tumor microenvironment[18]. CAR-T cell therapy works by enhancing the antitumor capacity of T cells. The overexpression of immune checkpoints limits the lethality of T cells. Immune checkpoint inhibitors may enhance the efficacy of CAR-T cell therapy since the inhibition of immune checkpoint expression increases the antitumor ability of T cells. Studies such as that by Cherkassky proved that the inhibition of the PD-1 receptor could weaken the inhibition of the PD-1 pathway in CAR-T cells, thus enhancing the ability of CAR-T cells[19]. A study showed that PD-L1 expression was upregulated in hepatocellular carcinoma cells exposed to GPC3 CAR-T cells, and the antitumor activity of CAR-T cells could be enhanced by the knockdown of the PD-1 gene[20]. Elise A. Chong *et al* reported a patient with refractory and recurrent diffuse large B-cell lymphoma. He received a PD-1 inhibitor 28 days after CAR-T cell treatment, after which the tumor cells shrank significantly. The patient was followed up for 12 mo, at which point sustained remission was achieved[21]. Wang *et al* also reported a case of refractory follicular lymphoma(FL) treatment. After 6 cycles of chemotherapy, the patient was diagnosed with refractory FL, and the results were poor. The patient was treated with CD19 CAR-T cells in combination with a reduced dose of nivolumab. To date, the patient has maintained CR for 16 mo[22]. Lu Zhang *et al* showed a case of refractory diffuse large B-cell lymphoma that developed disease progression after 12 wk of CAR-T cell treatment. Then, the patient was treated with a PD-1 inhibitor. To date, the patient has maintained CR[23]. Relevant literature reports were made by retrieving relevant literature at home and abroad (Figure 5). In this article, the patient relapsed 6 mo after CAR-T cell therapy. PD-1 inhibitors were still effective, and CAR-T cells could still be detected in the patient 2 years later. These findings suggest that PD-1 inhibitors may affect the efficacy of CAR-T cell therapy in the tumor microenvironment of immune suppression.

CONCLUSION

CAR-T cells have been widely used to treat hematological malignancies, but their associated remission rates still need improvement. Immune checkpoint inhibitors can vastly alter the immunosuppressive microenvironment where CAR-T cells live, improving their proliferative activity and antitumor capacity and increasing the prognosis of relapsed refractory tumors. Even after the failure of CAR-T therapy, the choice of PD-1 inhibitor therapy may still be effective. Our center will continue to treat patients who have failed CAR-T therapy with PD-1 inhibitors to explore the therapeutic feasibility of this treatment option and to provide new treatment strategies for relapsed refractory lymphoma.

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