CAR-T cell therapy in evolving therapeutic landscape of relapsed or refractory primary mediastinal B-cell lymphoma (PMBCL): challenges and aspirations — two case reports

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ABSTRACT

Chimeric antigen receptor T-cell (CAR-T) therapy is a promising option in patients with r/r PMBCL as a radical approach or a part of combined modality treatment. However, failure after CAR-T poses challenges to clinicians. The report presents two cases of patients with r/r PMBCL who received CAR-T therapy following several lines of chemotherapy. The first patient remains in complete metabolic remission 20 months after CAR-T infusion. The second case depicts the use of CAR-T in a combined treatment with bridging therapy to allogeneic haematopoietic stem cell transplantation (allo-HSCT). Combining radiotherapy with pembrolizumab remains a promising salvage therapy in patients who progressed or relapsed after CAR-T. Allo-HSCT is considered a viable consolidation strategy for young and fit patients with r/r disease who respond to bridging therapy. The ideal combination of CAR-T with novel agents and allo-HSCT is still developing and needs to be explored in prospective randomized trials.

Keywords: R/R PMBCL, CAR-T, axi-cel, allo-HSCT, salvage therapy in R/R PMBCL

Previously categorized as a subtype of diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL) is now recognized as an independent entity by the WHO [1]. Historically, the treatment approach for PMBCL patients involved combined therapy utilizing R-CHOP and radiotherapy (RT). However, alternative intensified regimens have been explored due to the considerable toxicity associated with RT.

In recent years, DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) has become widely endorsed as first-line therapy for newly diagnosed PMBCL based on exceptional outcomes achieved without consolidative RT, resulting in a 5-year EFS (event-free survival) rate of 93% and OS (overall survival) of 97% [2]. Even though over 60% of patients with advanced disease can achieve a cure with frontline therapy, the prognosis is unfavourable for those with refractory or relapsed disease (r/r), with an ORR (overall response rate) of only 25% and a 2-year SR (2-year survival rate) of 15% [3, 4].

For r/r PMBCL limited to the mediastinum, RT alone may offer a potential cure. In other cases, high-dose chemotherapy followed by autologous stem cell transplantation (auto-HSCT) is the current recommended standard of care [5]. CAR-T improved r/r aggressive B-cell non-Hodgkin lymphoma (B-NHL) prognosis in terms of PFS (progression-free survival) and OS since it was approved as third-line therapy [6]. The pivotal CAR-T trials, namely ZUMA-1 and TRANSCEND-NHL-001, have also included patients with r/r PMBCL, utilizing axicabtagene ciloleucel (axi-cel) and lisocabtagene maraleucel (liso-cel) as therapeutic products [7, 8]. Still, only 30–40% of patients treated with CAR-T experience durable remission [9]. Several novel agents have been approved for the treatment of aggressive B-NHL [10]. Anti–PD–1 agents, such as nivolumab with or without brentuximab vedotin, pembrolizumab, and allogeneic haematopoietic stem cell transplantation (allo-HSCT), are considered viable treatment options due to their clinical effectiveness in r/r PMBCL [11–13]. The optimal sequencing of these therapies is still developing.

The report details two cases of patients with r/r PMBCL who received CAR-T therapy following several lines of chemotherapy as a radical approach or a part of combined modality treatment.

CASE 1

In April 2021, a 47-year-old female patient with an anterior mediastinal mass distorting the superior mediastinum that infiltrated the surrounding soft tissue and sternum, causing lytic destruction, was admitted to the hospital. She suffered from dysphagia and a "lump" without B symptoms at the initial diagnosis. Firstly, a biopsy of the mediastinal mass indicated a morphological similarity to DLBCL. Due to progressive severe clinical manifestation, the salvage chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) regimen was implemented. Subsequent diagnostic procedures confirmed a diagnosis of PMBCL, stage II bulky, based on the Lugano Staging Classification [14], R-IPI 2, without central nervous system involvement, and she started treatment with DA-EPOCH-R. The interim PET response assessment demonstrated a mediastinal mass reduction, and the chemotherapy was continued for six cycles. However, upon completion of the therapy, the disease progressed. Subsequently, the patient received two cycles of the R-GDP regimen (rituximab, gemcitabine, dexamethasone, and cisplatin). Upon re-evaluation, there was no significant PET response (Deauville score 4).

Due to the chemorefractory biology of the disease, the decision was made to transition to CAR-T treatment using axi-cel. In July 2022, the anti-CD19 CAR-T cells were infused after lymphodepletion with the FluCy regimen (fludarabine: 30 mg/m^2, days –3 to –1; cyclophosphamide: 500 mg/m^2, days –3 to –1). On day +2, the patient presented a fever, grade 1, according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading [15] as a symptom of the cytokine release syndrome (CRS), which was treated with three doses of tocilizumab (8 mg/kg per dose). However, the patient continued to experience fever and hypotension, necessitating intravenous fluids and vasopressors in the following days, leading to a diagnosis of grade 3 CRS. Treatment with dexamethasone (10 mg q6h) was initiated on day + 4. The patient's neurological status was assessed on the sixth day using the Effector Cell-Associated Encephalopathy (ICE) score, yielding a total of 8 points [1] due to impaired speech. A diagnosis of grade 1 immune effector cell-associated neurotoxicity syndrome (ICANS) was made but fully resolved within the first 24 hours with the administration of glucocorticosteroids (GCS). The CRS symptoms ceased on day +8, and the patient did not require admission to the Intensive Care Unit (ICU).

On day +30, after the CAR-T cell infusion, the patient achieved a complete metabolic response (CMR) in PET scan evaluation. Prolonged hypogammaglobulinemia during the first 180 days after the CAR-T cell infusion required IVIG supplementation. At 20 months post-CAR-T treatment, the patient remains in CMR, with an ECOG score of 0, and continues to have follow-up appointments every three months.

CASE 2

A 23-year-old female patient presented with a bulky lesion localized in the mediastinum (IIE, R-IPI 1), without central nervous system involvement, was diagnosed in 2021. The patient did not report comorbidities. Initially, the patient was treated with three courses of DA-EPOCH-R. Due to the resistance, two courses of R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) and a cycle of R-GDP were administered. In the assessment of PET, the disease persisted progressive, Deauville score of 5. The patient was qualified for CAR-T therapy. The lymphodepletion with FluCy preceded axi-cell infusion and was implemented in April 2022.

Symptoms of CRS — fever and tachycardia — classified as grade 2 occurred on day +1. Based on the standard of care, symptomatic treatment was implemented and combined with four doses of tocilizumab and dexamethasone (10 mg q6h). On day + 4, the patient presented symptoms of ICANS, including severe disorders of consciousness and motor aphasia — grade 3, with an ICE score of 6 points. The patient required admission to the ICU. The symptoms resolved after administering a high dose of 1000 mg methylprednisolone. Treatment was continued with a gradual GCS dose reduction.

PET showed progression in the early assessment on day + 30 (Deauville score 5). The patient was qualified for combined salvage therapy with RT and pembrolizumab to bridge to allo-HSCT. After RT, the PET scan demonstrated partial remission. Subsequently, after five courses of pembrolizumab, the patient achieved a CMR.

In April 2023, allo-HSCT from an unrelated matched donor was performed after conditioning with FluBen-R (fludarabine, bendamustine, and rituximab). The graft versus host disease (GvHD) prophylaxis included tacrolimus, methotrexate, and thymoglobulin. In the early post-transplant period, fever was observed and successfully treated with empirical antibiotic therapy and supportive treatment. The reconstitution of granulopoiesis was achieved on day +18. On day +160, the patient presented symptoms of gastrointestinal GvHD — diarrhoea — grade 2 according to the MAGIC score [16], and required hospitalization and 1st line therapy with glucocorticoids, which was conducted successfully.

Two hundred twenty days post-allo-HSCT and 20 months after CAR-T cell infusion, the patient persisted in CMR according to PET assessment, ECOG 0, with 100% donor chimerism, and requires occasional supplementation of IVIG.

DISCUSSION

In two patients, the authors describe the different places of cellular immunotherapy with CAR-T in the therapeutic strategy of PMBCL, which is resistant to standard chemoimmunotherapy.

The first case provides evidence of the efficiency of CAR-T in achieving long-lasting complete remission in r/r PMBCL. CAR-T has dramatically changed the treatment landscape of B-NHL, including PMBCL [7, 8]. CART-SIE, the

first real-life study comparing the prognosis of patients affected by r/r PMBCL and DLBCL treated with axi-cel, revealed a superiority OS and PFS for PMBCL with a similar incidence of CRS and ICANS [17]. Proper primary assessment for this therapy inclusion seems to be a core issue. Among potential factors, i.a., CAR-T-cell type (axi-cel better), primary refractory, no previous HSCT, a more significant number of pre–CAR-T therapies, increased tumour burden, high LDH, IL-6, CRP, and ferritin level, unfavourable R-IPI, age, and time to CAR-T failure < 30 days were predictive of inferior outcomes and CAR-T failure [18–20]. Only two lines of prior treatment in the first case compared to much chemorefractory disease in the second one with early failure could have fundamental significance in better response. Practical cooperation with the transplant centre plays a vital role in successfully using CAR-T with manageable safety. This is particularly crucial due to the possibility of life-threatening complications that may necessitate the expertise of various specialists, such as neurologists, intensivists, cardiologists, and radiologists.

The second case presents the use of CAR-T in a combined modality approach with bridging therapy to allo-HSCT. Despite advancements in CAR-T therapy, failure after infusion and relapse rates are high, reaching 66% [18]. Various alternative treatment strategies, such as monoclonal antibodies, antibody-drug conjugates, bispecific antibodies, immunomodulatory drugs, checkpoint inhibitors, molecular pathway inhibitors, and epigenetic-modifying molecules, have been explored for r/r B-NHL [21].

CAR-T cell exhaustion, resulting from repeated stimulation, causes reduced multiplication, impaired tumour-fighting efficacy, and decreased persistence, leading to nonresponse and relapse [22]. Retrospective studies generated discrepancies in the use of consolidative mediastinal RT in PMBCL when combined with standard-dose chemoimmunotherapy [23]. Emerging evidence suggests that combining it with immunotherapy might enhance the abscopal effect. RT stimulates an anti-tumour immune response through various mechanisms, including the upregulation of MHC-1, secretion of pro-inflammatory cytokines, and neoantigens generation [24]. PD1 inhibitors have the potential to amplify this effect through immune-mediated impact in lymphoma [25]. Pembrolizumab, a single-agent PD-1 inhibitor, has shown high and long-lasting remission rates in relapsed lymphoma [26]. The binding of PD-1 to its receptor, PD-L1, on immune cells negatively regulates T-cell-mediated immune events. Therefore, blocking the PD-1/PD-L1 signalling pathway was considered a viable cancer therapy. The overexpression of PD-L1 in 30–80% of PMBCL cases supports using pembrolizumab blockade in this disease [27]. On June 13, 2018, the FDA granted accelerated approval to pembrolizumab for the treatment of adult and paediatric patients with PMBCL, or those who have relapsed after two or more prior lines of therapy based on the early results of the KEYNOTE-170 study, which confirmed the efficacy and safety of pembrolizumab in patients with r/r PMBCL with approximately four years of follow-up [28]. Given the frequent upregulation of PD-1 and PD-L1 on CAR-T cells in the blood and lymphoma microenvironment of relapsing patients, there has been promising research on reversing the exhausted state of CAR-T cells through PD-1 inhibition [29, 30].

Combinatory therapy led to CMR and successful consolidation with allo-HSCT in the present patient. Allo-HSCT would provide a potent curative modality in patients with r/r aggressive B-NHL, including PMBCL [11, 31–33]. Nevertheless, CAR-T has gained prominence over allo-HSCT in current clinical practice due to its efficacy and safety profile. It is considered a potential salvage option for patients who experience treatment failure after CAR-T. Integrating allo-HSCT and CAR-T therapy has been actively investigated with promising results. Three clinical scenarios can be considered: allo-HSCT before CAR-T, allo-HSCT after CAR-T progression/relapse, or tandem CAR-T/allo-HSCT sequence with CAR-T as induction therapy, as proposed for acute lymphoblastic leukaemia. Recently, Zurko et al. reported data on allo-HSCT following CAR-T in 88 patients, with 1-year NRM (non-relapse mortality), PFS, and OS rates of 22%, 45%, and 59%, respectively [34]. Similarly, another study involving 39 adult patients showcased a 2-year NRM rate of 26% and relapse/progression incidences of 43%, with the 2-year OS and PFS of 45% and 31%, respectively [35]. Interestingly, prior failure of CAR-T therapy does not appear to impact the outcomes of allo-HSCT significantly, but sufficient disease control before transplantation is crucial for long-term outcomes [31, 32]. For r/r PMBCL patients at high risk of failure, CAR-T-cell therapy can be planned upfront as induction therapy to obtain CR or reduce the lymphoma burden as much as possible to improve the results of allo-HSCT. Limited data exist on the safety, efficacy as well as predictive factors of allo-HSCT after CAR-T therapy in r/r PMBCL, mainly derived from case reports. Prospective studies should be conducted to define the best approach and improve the outcome of r/r PMBCL patients.

CONCLUSIONS

CAR-T therapy is a promising option for managing r/r PMBCL as a curative, bridging, conditioning, or consolidation treatment. Failure after CAR-T cell treatment remains a significant concern, representing an unmet medical requirement. It is advisable to consider CAR-T therapy earlier for individuals with high resistance to minimize the cumulative toxicities of other systemic treatments and enhance T-cell fitness. More data must be collected on the optimal sequencing of therapies for patients who experience disease progression after CAR-T therapy. Combining RT with pembrolizumab presents a promising salvage therapy. Allo-HSCT can be a viable consolidation strategy for young and fit patients with r/r disease who respond to bridging therapy. The ideal combination of CAR-T with novel agents and allo-HSCT needs to be explored in prospective randomized trials.

Article information and declarations

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