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Primary refractory primary mediastinal lymphoma treated with CAR-T: new possibilities and challenges

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Introduction

Chimeric antigen receptors T-cells (CAR-T) are autologous, genetically engineered T-cells redirected against a specific antigen. Indications for the use of CAR-T include refractory and relapsed (R/R), large B-cell lymphoma (LBCL), acute lymphoblastic leukemia, mantle cell lymphoma, follicular lymphoma, and multiple myeloma.

Primary mediastinal lymphoma (PMBCL) represents 2–3% of non-Hodgkin lymphomas (NHL), with 10–30% of patients having primary refractory or relapsed disease [1]. The SCHOLAR-1 study reported outcomes of R/R LBCL treatment enabling complete response (CR) achievement only in 7% of cases, among 26% OR [2]. However, superior outcomes with novel therapies emerging are possible. The ZUMA-1 axicabtagene ciloleucel (axi-cel) registration trial reported 52% CR with an 82% overall response (OR) rate in this setting [3].

This clinical vignette highlights the therapeutic opportunities created by CAR-T, and looks at ways of enhancing and sustaining responses and managing severe therapy-associated events.

Patient and treatment

A 39-year-old male patient presented with a bulky lesion located in the mediastinum, infiltrating and exceeding the chest wall (Lugano IV), diagnosed in March 2019. The patient progressed after first-line treatment with dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)-rituximab and second-line with DHAP (dexamethasone, cytarabine, cisplatin)-rituximab, and was qualified for CAR-T therapy. After successful lymphocyte collection, due to disease activity and risk of progression awaiting manufacturing process, BR (bendamustine, rituximab) bridging therapy was implemented. FluCy (fludarabine, cyclophosphamide) lymphodepletion preceded axi-cell infusion. The extrathoracic tumor regressed during the primary 14 days post-infusion, becoming imperceptible (Figure 1).

CAR-T-specific adverse events occurred, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). CRS, classified as grade 3 according to American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading for CRS [4], occurred on day 2, presenting as fever, tachycardia, and hypotension. Based on the standard of care in G3 CRS, symptomatic treatment was implemented and combined with four doses of tocilizumab (8 mg/kg on each dose) started on day 5. Grade 4 ICANS occurred on day 5, presenting as graphomotor disorders with features of cerebral edema in computed tomography (CT). The neurological condition was assessed using the Effector Cell-Associated Encephalopathy (ICE) score [4]. The patient was admitted to the ICU treated with dexamethasone 10 mg every 6 hours and then a methylprednisolone dose of 1,000 mg and sodium valproate dose 2 × 600 mg. Symptoms subsided on day 10, and the patient was referred to the hematology department. On day 12, ICANS recurred following discontinuation of glucocorticosteroids, presenting as motor aphasia and depressed level of consciousness, with features of cerebral edema in CT. Re-admission to ICU and restoration of methylprednisolone treatment resulted in the resolution of symptoms on day 14.

30 days post-infusion, a positron emission tomography (PET) scan showed a partial metabolic response (Deauville Scale 4) (PR, partial response). Due to active residual disease 60 days post-infusion, the patient was referred for mediastinum radiotherapy (20 × 2 Gy). Recurrent fever and abnormal thoracic CT scan following radiotherapy raised

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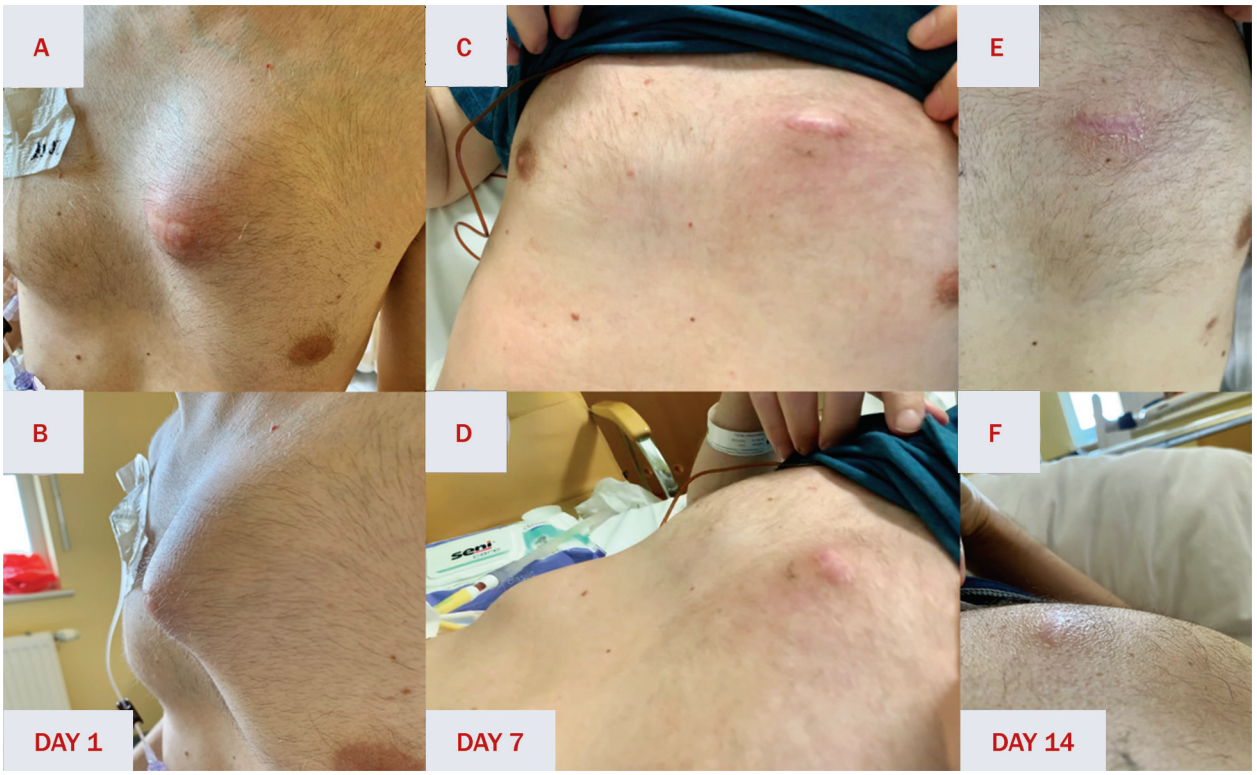

Figure 1. Extrathoracic tumor regression following chimeric antigen receptors T-cells (CAR-T) infusion: **A**, **B**. Large lesion exceeding chest wall on day of axi-cel infusion; **C**, **D**. Tumor regression 7 days post-infusion; **E**, **F**. 14 days after CAR-T infusion, umor is almost imperceptible

a suspicion of invasive fungal disease (IFD). CAR-T therapy increases the risk of infectious complications [3, 5, 6]. Broad-spectrum antibiotic therapy and liposomal amphotericin B resulted in clinical improvement. Due to a bronchopleural fistula found in bronchofiberoscopy, an upper left lobectomy was performed, although histological examination excluded IFD and NHL. Compared to allogeneic hematopoietic cell transplantation (allo-HCT), the incidence of IFDs after CAR-T is rare [5–7]. 180 days post-infusion, the patient achieved complete metabolic response (Deauville Scale 3) (CR).

In November 2020, with persisting CR, 10/10 human leukocyte antigen (HLA)-matched sibling HCT (hematopoietic cell transplantation) with BendaFlu (bendamustine, fludarabine) reduced-intensity conditioning was implemented. Graft-vesus-host disease (GvHD) prophylaxis included cyclosporin A, thymoglobulin, and methotrexate. Hematological recovery was observed on day 14. On day 3 post-allo-HCT, fever and cough occurred, diagnosed as coronavirus disease 2019 (COVID-19). Remdesivir and plasma of convalescent application resulted in resolution of symptoms within 48 h. Cutaneous grade 2 GvHD occurred on day 48. 90 days post-HCT, the patient persisted in CR, Eastern Cooperative Oncology Group (ECOG) Performance Status Scale 0 without symptoms of GvHD with 100% donor chimerism. The recent assessment in February 2022 confirmed CR.

Discussion

CAR-T therapy is a powerful tool in R/R lymphomas treatment, and in this case, resulted in the achievement of immediate disease control leading to PR and enabling effective allo-HCT. Despite a high CR rate, there is still up to a 60% risk of progression or relapse after CAR-T therapy of R/R LBCL. Thus, allo-HCT could be considered to achieve sustainability of response, especially in patients without CR at 30 days post-infusion [8]. Relapses often occur in known pretreatment sites [9]. Therefore, radiotherapy to high-risk lesions could be considered. Also, bridging with radiotherapy prior to CAR-T infusion is an option [10]. Nevertheless, the role of radiotherapy post-CAR-T infusion remains undefined. New strategies and management standardization for responding patients are needed.

The risk of severe adverse events highlights the requirement for complex care and specialized centers prepared to manage them [5]. In the ZUMA-1 trial, CRS occurrence was 93%, and ICANS 64%. However, respectively, only 13% and 28% of cases were G3 or higher [3]. Currently, early use of tocilizumab in CRS and steroids in ICANS is recommended [10].

Considering that CAR-T is a still developing yet successful technology with further indications expanding, this approach will play a significant part in treating hematological

malignancies. Complications might be life-threatening and complex but, due to standardized algorithms, they are now manageable.

Authors' contributions

All authors — data collection, analysis, writing, and manuscript acceptance.

Conflict of interest

None.

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None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to biomedical journals.

References

1. Lees C, Keane C, Gandhi MK, et al. Biology and therapy of primary mediastinal B-cell lymphoma: current status and future directions. Br J Haematol. 2019; 185(1): 25–41, doi: 10.1111/bjh.15778, indexed in Pubmed: 30740662.
2. Crump M, Neelapu S, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017; 130(16): 1800–1808, doi: 10.1182/blood-2017-03-769620.
3. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017; 377(26): 2531–2544, doi: 10.1056/NEJMoa1707447, indexed in Pubmed: 29226797.
4. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019; 25(4): 625–638, doi: 10.1016/j.bbmt.2018.12.758, indexed in Pubmed: 30592986.
5. Gil L, Łojko-Dankowska A, Matuszak M, et al. CAR-T cell therapy — toxicity and its management. Acta Haematol Pol. 2020; 51(1): 6–10, doi: 10.2478/ahp-2020-0003.
6. Jain T, Bar M, Kansagra AJ, et al. Use of chimeric antigen receptor T cell therapy in clinical practice for relapsed/refractory aggressive B cell non-Hodgkin lymphoma: an Expert Panel Opinion from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant. 2019; 25(12): 2305–2321, doi: 10.1016/j.bbmt.2019.08.015, indexed in Pubmed: 31446199.
7. Girmenia C, Raiola AM, Piciocchi A, et al. Incidence and outcome of invasive fungal diseases after allogeneic stem cell transplantation: a prospective study of the Gruppo Italiano Trapianto Midollo Osseo (GITMO). Biol Blood Marrow Transplant. 2014; 20(6): 872–880, doi: 10.1016/j.bbmt.2014.03.004, indexed in Pubmed: 24631738.
8. Al Zaki A, Feng L, Watson G, et al. Day 30 SUVmax predicts progression in patients with lymphoma achieving PR/SD after CAR T-cell therapy. Blood Adv. 2022; 6(9): 2867–2871, doi: 10.1182/bloodadvances.2021006715, indexed in Pubmed: 35015825.
9. Figura NB, Robinson TJ, Sim AJ, et al. Patterns and predictors of failure in recurrent or refractory large B-cell lymphomas after chimeric antigen receptor T-cell therapy. Int J Radiat Oncol Biol Phys. 2021; 111(5): 1145–1154, doi: 10.1016/j.ijrobp.2021.06.038, indexed in Pubmed: 34242714.
10. Hayden PJ, Roddie C, Bader P, et al. Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA). Ann Oncol. 2022; 33(3): 259–275, doi: 10.1016/j.annonc.2021.12.003, indexed in Pubmed: 34923107.