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CASE REPORT

# Chimeric antigen receptor T-cell therapy for refractory post-transplant lymphoproliferative disorder after lung transplantation

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Chimeric antigen receptor T-cell therapy (CAR-T) has been used to treat refractory post-transplant lymphoproliferative disorder (PTLD) in solid organ transplant patients, including heart, kidney, liver, intestine, and pancreas. We report the use of CAR-T for treating refractory PTLD in a 73-year-old female who was 7 years post bilateral lung transplantation for idiopathic pulmonary fibrosis. We discuss the immunosuppression management in this patient, as well as her clinical course and outcome.
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## Background

Chimeric antigen receptor T-cell therapy (CAR-T) has been used to treat refractory post-transplant lymphoproliferative disorder (PTLD) in solid organ transplant patients, including heart, kidney, liver, intestine, and pancreas.[1,2] We report the use of CAR-T for treating refractory PTLD in a 73-year-old female who was 7 years post bilateral lung transplantation for idiopathic pulmonary fibrosis (IPF). We discuss the immunosuppression management in this patient, as well as her clinical course and outcome.

## Case report

A 66-year-old female underwent bilateral lung transplantation for IPF. She made an excellent clinical recovery after transplantation. Her immunosuppression regimen included tacrolimus, prednisone, and azathioprine—she had previously not tolerated mycophenolate because of gastrointestinal symptoms. Her allograft function remained stable with a forced expiratory volume in 1 second of 2.2 liter and no evidence of chronic lung allograft dysfunction. Her Epstein-Barr virus status was donor positive, recipient positive, and her CMV status was donor positive, recipient positive. She had no other relevant post-transplant medical history.

Approximately 6.5 years after transplant, at age 73, she developed fatigue, weight loss, low-grade fever, and gastrointestinal symptoms. She was found to have massive lymphadenopathy in her abdomen, chest, and neck (Figure 1). An excisional cervical lymph node biopsy confirmed monomorphic PTLD, diffuse large B-cell lymphoma, germinal center type. She had extra-nodal disease in the peritoneum, small bowel, and skeleton identified on positron emmision tomography/computed tomography scan, consistent with Ann Arbor stage IV. At the time of diagnosis, her lactate dehydrogenase was > 500 and she had evidence of tumor lysis

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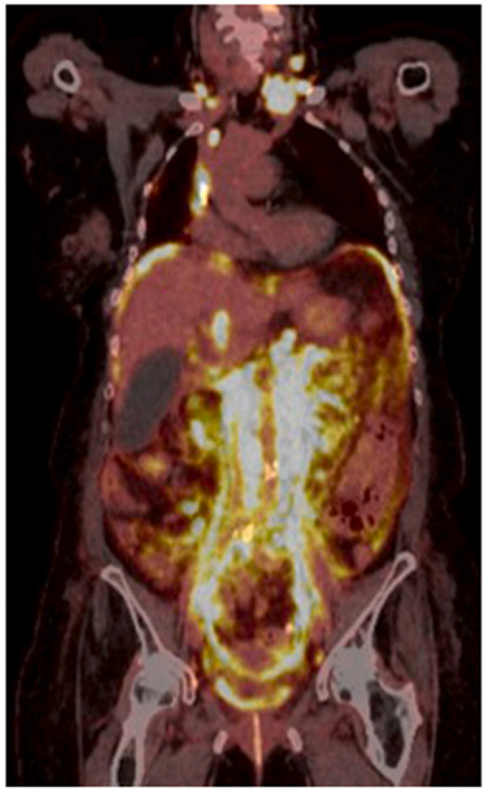

**Figure 1** PET-CT showing intense 18-fluoro-deoxyglucose (FDG) avidity in the cervical, supraclavicular, mediastinal, retroperitoneal, and mesenteric lymph nodes at the time of diagnosis.

syndrome. The lymphoma was Epstein-Barr virus-encoded RNA negative on biopsy, and her serum Epstein-Barr virus polymerase chain reaction was negative.

Azathioprine was discontinued and the tacrolimus trough target was reduced to 3 to 5 ng/ml. She underwent treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, initially with a 50% dose reduction because of her ongoing immunosuppression and perceived risk of infection. Her florid symptomology, high disease burden, and highly elevated lactate dehydrogenase level led to the clinical decision to begin treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone rather than the less intensive rituximab monotherapy. She had a complete metabolic response and was continued on rituximab monotherapy.

Five months later, she developed biopsy-proven recurrent/refractory disease in the left mid-back (Figure 2, left). She underwent radiation therapy to a dose of 20 Gray in 5 fractions to the left T9 to T10 posterior rib area. She was admitted to the hospital and started on fludarabine 15 mg/m$^2$ intravenous (IV) (50% dose reduced because of kidney disease) and cyclophosphamide 500 mg/m$^2$ IV in preparation for CAR-T. Once her leukocyte count dropped below 2,000/mm$^3$ from induction chemotherapy, tacrolimus was discontinued. She was treated with axicabtagene ciloleucel (anti-CD19 CAR-T). She was treated with dexamethasone 10 mg daily concurrent with CAR-T administration. She developed cytokine release syndrome (CRS) grade 2 (as defined by American Society for Transplantation and Cellular Therapy consensus criteria)[3] and immune effector cell-associated neurotoxicity syndrome (ICANS) grade 2 and was treated with dexamethasone and tocilizumab. CRS and ICANS symptoms both lasted 9 days. Once her leukocyte count recovered to above 2,500/mm$^3$, her tacrolimus was restarted (goal 3-5 ng/ml). She was off tacrolimus for a total of 25 days, though during this time, she received dexamethasone and tocilizumab for treatment of CRS and ICANS.

Valacyclovir was administered for herpes, cytomegalovirus (CMV), and varicella prophylaxis, and she received 30 days of fluconazole for antifungal prophylaxis. IV pentamidine was administered once for pneumocystis prophylaxis. Valganciclovir had been previously discontinued as is our standard practice in donor-positive, recipient-positive patients who have had no CMV reactivations or breakthrough infections and are at least 1-year post-lung transplant. Serial serum CMV polymerase chain reaction was monitored for reactivation because of the weak action of valacyclovir against CMV. She was found to have low immunoglobulin G (410 mg/dl) following CAR-T administration. One dose of IV immunoglobulin was administered as a preventive measure.

She had a complete metabolic response to CAR-T therapy (Figure 2, right). During her hospitalization, she required supplemental oxygen because of CRS and volume overload, but upon hospital discharge, she was on room air.

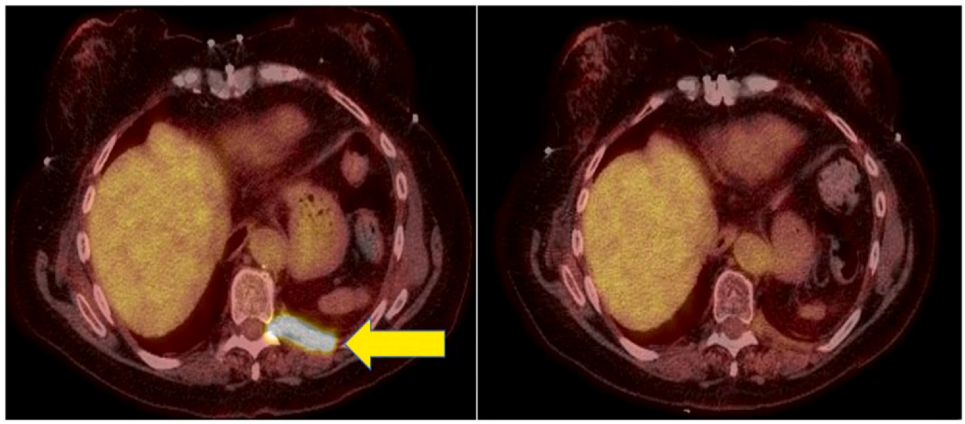

**Figure 2** (Left): Pre-CAR-T PET-CT showing area (yellow arrow) of refractory disease in the left ninth intercostal space. (Right): 90-day post-CAR-T PET-CT showing resolution of the previously seen area of uptake in the left ninth intercostal space.

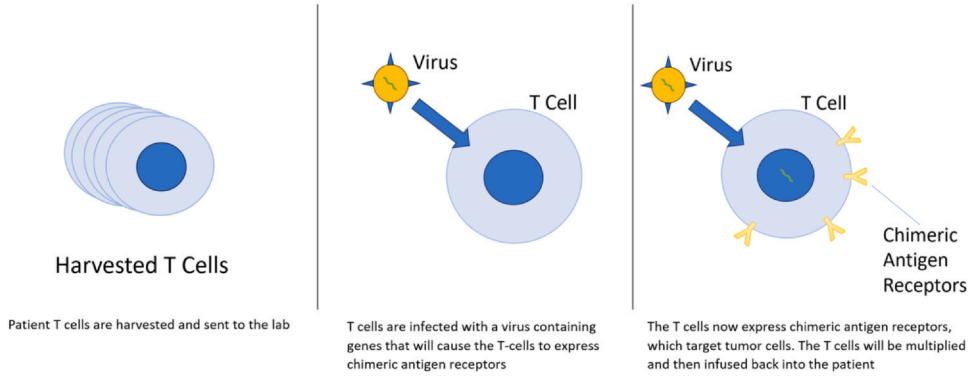


**Figure 3** Diagrammatic representation of the production and function of CAR-T cells. CAR-T, chimeric antigen receptor T-cell therapy.

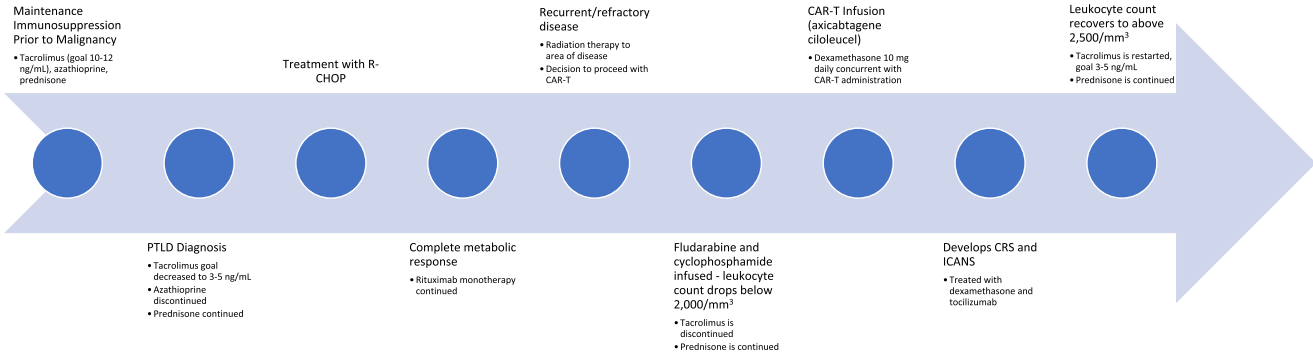


**Figure 4** Timeline of changes in immunosuppression.

Twelve months after CAR-T treatment, her allograft function remained at baseline with an forced expiratory volume in 1 second of 2.2 liter and no evidence of chronic lung allograft dysfunction. She did not experience any clinical episodes of lung allograft rejection. Surveillance biopsies were not performed due to a lack of clinical indication for them. She remains in remission. Since undergoing CAR-T, she has had a urinary tract infection but otherwise no other infectious complications.

## Summary

We report the use of CAR-T *(*Figure 3) for treating refractory PTLD in a 73-year-old female who was 7 years post bilateral lung transplantation for IPF. Traditional treatment for relapsed/refractory PTLD includes salvage chemotherapy and autologous stem cell transplant. However, prior data show treatment-related mortality is high and outcomes are modest.[4] With the emergence of CAR-T in the second line of treatment for refractory diffuse large B-cell lymphoma showing an overall survival benefit over salvage chemotherapy and autologous stem cell transplant,[5] CAR-T was felt to be the preferable choice. The outcome of our patient is comparable to other solid-organ transplant patients who have received CAR-T for PTLD post-transplant in that she experienced CRS (82%) and ICANS (73%), did not experience allograft rejection (86%), and had a complete response (55%). In addition, all immunosuppression was stopped before CAR-T infusion, similar to other cases (64%).[1]

CAR-T therapy is a possible option for treatment of refractory PTLD in the setting of lung transplantation. CAR-T may increase the risk of allograft recognition[1] but did not result in allograft dysfunction in our patient. Immunosuppression may limit the effectiveness of CAR-T,[6,7] so withholding calcineurin inhibitors for a period may be indicated, both before and post-CAR-T. Management of immunosuppression *(*Figure 4*)* in the peri-CAR-T period should be done as part of a multidisciplinary treatment approach.

## Disclosure statement

U.F. has received consulting fees from Morphosys and honoraria from Kite Pharma and Caribou. The remaining authors of this manuscript have no conflicts of interest to disclose.

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## Patient consent

The authors confirm that appropriate patient consent to publish this case report was received.

## Author Contributions

K.V. prepared the manuscript. K.V., T.P., J.K.T., E.M., and U.F. reviewed and edited the manuscript.

## References


1. McKenna M, Epperla N, Ghobadi A, et al. Real-world evidence of the safety and survival with CD19 CAR-T cell therapy for relapsed/refractory solid organ transplant-related PTLD. Br J Haematol 2023;202:248-55. https://doi.org/10.1111/bjh.18828.
2. Krishnamoorthy S, Ghobadi A, Santos RD, et al. CAR-T therapy in solid organ transplant recipients with treatment refractory post-transplant lymphoproliferative disorder. Am J Transplant 2021;21:809-14. https://doi.org/10.1111/ajt.16367.
3. 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;25:625-38. https://doi.org/10.1016/j.bbmt.2018.12.758. Epub 2018 Dec 25. PMID: 30592986.
4. Eyre TA, Caillard S, Finel H, et al. Autologous stem cell transplantation for post-transplant lymphoproliferative disorders after solid organ transplantation: a retrospective analysis from the Lymphoma Working Party of the EBMT. Bone Marrow Transplant 2021;56:2118-24. https://doi.org/10.1038/s41409-021-01270-5.
5. Westin JR, Oluwole OO, Kersten MJ, et al. Survival with axicabtagene ciloleucel in large b-cell lymphoma. N Engl J Med 2023;389:148-57. https://doi.org/10.1056/NEJMoa2301665.
6. Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med 2014;6:224ra25. https://doi.org/10.1126/scitranslmed.3008226. PMID: 24553386; PMCID: PMC4684949.
7. Strati P, Ahmed S, Furqan F, et al. Prognostic impact of corticosteroids on efficacy of chimeric antigen receptor T-cell therapy in large B-cell lymphoma. Blood 2021;137:3272-6. https://doi.org/10.1182/blood.2020008865. PMID: 33534891; PMCID: PMC8351896.