Chapter 48
Post-Transplant Lymphoproliferative Disorders: Management

Sambhavi Krishnamoorthy and Tarek Alhamad

Introduction

Post-transplant lymphoproliferative disorders (PTLD) are a heterogeneous group of disorders that could present as indolent hyperplasia or aggressive lymphomas with distinct pathological subtypes and variable clinical presentations (Table 48.1). Increased incidence of late-onset EBV negative monomorphic PTLD associated with therapeutic immunosuppression has been observed with solid organ transplant recipients [1]. Advances in chemotherapeutic agents and cell therapy in the management of PTLD have made a significant impact on patient outcomes, given the significant morbidity and mortality related to this complication. In this chapter, we review a case of PTLD to understand the risks and benefits of treating this challenging disease and the serious impact it has in solid organ transplantation.

The patient is a 57-year-old woman with a history of end-stage kidney disease (ESKD) due to IgA nephropathy who received a deceased donor kidney transplant in 2005. The induction agent was anti-thymocyte globulin, and maintenance immunosuppression consisted of mycophenolic acid, tacrolimus, and prednisone. Fifteen years after kidney transplantation patient developed persistent nausea, satiety, and weight loss. She underwent a CT scan of her abdomen/pelvis that showed a large infiltrative mass in the left pelvis 10 × 15 cm continuous with retroperitoneal

S. Krishnamoorthy (✉)
Division of Nephrology, University of Chicago, Chicago, IL, USA
e-mail: samk@medicine.bsd.uchicago.edu

T. Alhamad
Division of Nephrology, Department of Medicine, Washington University School of Medicine, St. Louis, MO, USA
e-mail: talhamad@wustl.edu

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2022

F. Aziz, S. Parajuli (eds.), *Complications in Kidney Transplantation*,
https://doi.org/10.1007/978-3-031-13569-9_48

Table 48.1 WHO classification of PTLD

Benign polyclonal lymphoproliferation
Florid follicular hyperplasia
Polymorphic PTLD
Monomorphic PTLD
Diffuse large B cell lymphoma
Burkitt lymphoma
Plasma cell neoplasm
Peripheral T cell lymphoma, not otherwise specified
Classic Hodgkin lymphoma type PTLD

WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised fourth edition, Swerdlow SH, Campo E, Harris NL, et al. (Eds), International Agency for Research on Cancer (IARC), Lyon 2017

lymphadenopathy. A biopsy of the mass was consistent with EBV (Epstein–Barr virus) negative, non-germinal center B-cell-like (non-GCB), diffuse large B cell lymphoma (DLBCL).

Question 1
What is the best treatment strategy for this patient?

A. Reduction in immunosuppression as first-line therapy.
B. Reduction in immunosuppression with rituximab.
C. Reduction in immunosuppression with rituximab with or without sequential or concomitant chemotherapy.
D. Chimeric antigen receptor T cell (CAR-T) therapy.

The correct answer is C.

Reducing immunosuppression with or without rituximab is usually the first-line therapy for early or minimally symptomatic PTLD. But for monomorphic PTLD, with significant symptoms, a combination of rituximab with or without sequential R- CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) therapy with a reduction in immunosuppression is recommended based on PTLD-1 trial [2]. CAR-T therapy is usually considered after the failure of first- and second-line salvage therapy.

Clinical Course

The patient's antimetabolite and tacrolimus were stopped as she received 4 cycles of R-CHOP chemotherapy with incomplete response noted on follow-up PET scan done 3 months later. Subsequently, the patient received 3 cycles of R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) salvage therapy, with continued failure to reach clinical remission. A decision was made to proceed with CAR-T

therapy. The patient underwent leukapheresis followed by lymphodepletion therapy and CAR-T infusion. On day 2 of CAR-T infusion, the patient developed a high-grade fever of 102.5 F and developed hypotension with a BP of 80/50.

Question 2
What is the most likely cause of the patient's fever and hypotension?

A. Sepsis, likely bacteremia due to immunosuppression from chemotherapy.
B. Serum sickness from CAR-T infusion.
C. Acute pyelonephritis of allograft.
D. Cytokine release syndrome.

The correct answer is D.

In autologous CAR-T therapy, T cells are separated from a patient's blood using apheresis. These cells are then genetically modified to express chimeric surface antigen receptors. In the currently approved CARs, these receptors allow the T cells to recognize and bind a tumor targeting the pan B-cell marker CD19. Though sepsis and pyelonephritis would be considered in the differential, cytokine release syndrome (CRS) is the most common adverse reaction noted after CAR-T therapy, with an incidence ranging from 35 to 93% [3]. CAR-T does not cause serum sickness.

Additional Clinical Course

The patient received tocilizumab for severe cytokine release syndrome. Her post-CAR-T course was also complicated by ICANS (immune effector cell-associated neurotoxicity syndrome), for which she received steroids and seizure prophylaxis. She ultimately developed aspiration pneumonia with pseudomonas aeruginosa requiring intubation and mechanical ventilation due to hypoxia. She required vasopressors for a septic shock as well. She developed acute kidney injury requiring kidney replacement therapy. The patient developed refractory shock despite treatment with broad-spectrum antibiotics and vasopressors. The family decided to pursue comfort care.

Discussion

PTLD is a devastating and potentially fatal long-term complication associated with immunosuppression and/or EBV infection in solid organ transplant patients. The overall incidence of PTLD is about 20% in SOT recipients, and the incidence varies by organs, with intestinal and multiorgan transplants having the highest risk and kidney transplants having the lowest risk. Early-onset PTLD is usually EBV associated and polymorphic, whereas late-onset PTLD is usually EBV negative and

monomorphic. Though about 90% PTLDs originate from B cells, in the minority, they could be of T cell or null cell origin as well [1]. Reduction in immunosuppression remains the cornerstone of therapy, especially for early PTLD. Outcomes for PTLD of B cell origin have substantially improved with the introduction of rituximab [4], and the subsequent PTLD trials show better survival with the combination of rituximab and chemotherapy [2]. Radiation therapy may be considered for CNS involvement. The reduction in immunosuppression must be balanced with the risk of allograft rejection and allograft loss. This decision is especially difficult in life-sustaining organs such as heart transplants.

Additionally, refractory PTLD continues to have inferior outcomes. Various strategies include salvage regimens such as R-ICE (rituximab, ifosfamide, carboplatin, and etoposide), R-GemOx (rituximab, gemcitabine, and oxaliplatin), and R-DHAX (rituximab, dexamethasone, cytarabine, and oxaliplatin) are usually employed as second-line therapy [1]. CAR-T therapy is an adoptive T cell therapy that was first studied in pediatric ALL and showed improved outcomes. It has shown a disease-free survival of 35–40% in 1–2 years after therapy with a complete response rate of 50% in DLBCL [5, 6]. CRS and ICANS are well observed common adverse reactions to CAR-T therapy [3, 7]. Dexamethasone, seizure prophylaxis with/without IL-6 antibody or IL-6 receptor antibody may be used to manage these adverse effects. Gupta et al. reported that CAR-T therapy is associated with AKI. The 60-day mortality in patients with acute tubular necrosis after CAR-T therapy was 67% [8]. A recent case series of 3 solid organ recipients who underwent CAR-T therapy for PTLD showed poor response to therapy and significant adverse effects [9]. Further research is needed to increase CAR-T efficacy with better strategies to manage their adverse effects and improve outcomes in refractory PTLD without affecting allograft outcomes in solid organ transplant recipients.

References

1. Dharnidharka VR, Webster AC, Martinez OM, Preiksaitis JK, Leblond V, Choquet S. Post-transplant lymphoproliferative disorders. Nat Rev Dis Primers. 2016;2:15088.
2. Trappe R, Oertel S, Leblond V, Mollee P, Sender M, Reinke P, et al. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial. Lancet Oncol. 2012;13(2):196–206.
3. Hirayama AV, Turtle CJ. Toxicities of CD19 CAR-T cell immunotherapy. Am J Hematol. 2019;94(S1):S42–S9.
4. Choquet S, Leblond V, Herbrecht R, Socié G, Stoppa AM, Vandenberghe P, et al. Efficacy and safety of rituximab in B-cell post-transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study. Blood. 2006;107(8):3053–7.
5. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531–44.
6. Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol. 2019;20(1):31–42.

7. Gust J, Hay KA, Hanafi LA, Li D, Myerson D, Gonzalez-Cuyar LF, et al. Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. Cancer Discov. 2017;7(12):1404–19.
8. Gupta S, Seethapathy H, Strohbehn IA, Frigault MJ, O'Donnell EK, Jacobson CA, et al. Acute kidney injury and electrolyte abnormalities after chimeric antigen receptor T-cell (CAR-T) therapy for diffuse large B-cell lymphoma. Am J Kidney Dis. 2020;76(1):63–71.
9. Krishnamoorthy S, Ghobadi A, Santos RD, Schilling JD, Malone AF, Murad H, et al. CAR-T therapy in solid organ transplant recipients with treatment refractory posttransplant lymphoproliferative disorder. Am J Transplant. 2021;21(2):809–14.