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Review

Management of Resistant Post-transplant Lymphoproliferative Disorder: CAR-T Is a New Option

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Abstract. *This is a review of the therapeutic options for resistant/refractory post-transplant lymphoproliferative disorder (PTLD) in relation to Chimeric antigen receptor-T cell (CAR-T) therapy. Out of a number of possible future strategies for the treatment of PTLD, the following methods were implemented in real-world practice: anti-PD1 therapy with checkpoint inhibitor nivolumab, new anti-CD20 ofatumumab, brentuximab vedotin, and zanubrutinib. However, for all these innovative methods, only individual cases of successful treatment of rituximab-resistant Epstein-Barr Virus (EBV)-PTLD patients have been reported so far. CAR-T is an innovative method of treatment, based on genetic modification of receptors of T autologous lymphocytes, creating the "living drug". This therapy can be potent against resistant PTLD, which is a lymphoproliferation of B-lymphocytes. The published real-world data of 17 patients treated with CAR-T for PTLD indicate a success rate of 76.5%. There is development of innovative methods of treatment of resistant/refractory PTLD, with high rate of resolution after CAR-T therapy.*

Post-transplant lymphoproliferative disorder (PTLD) is defined as uncontrolled proliferation of B-lymphocytes, occurring after hematopoietic cell transplantation (HCT) or solid organ transplantation (SOT), resulting from iatrogenic suppression of T-lymphocytes (1). In the majority of cases, particularly after HCT, lymphoproliferation is driven by Epstein-Barr Virus (EBV) persisting in a latent form in B-lymphocytes. However, due to impaired function of T-lymphocytes, latent EBV undergoes replication. In the SOT setting, some PTLDs are EBV-negative. EBV-related PTLD can be counted as a secondary malignancy, occurring early after transplantation, usually within the first six months after HCT, and up to several years after organ transplantation. In contrast, EBV-negative PTLD developing >5 years after SOT, should be regarded as a typical non-Hodgkin lymphoma (NHL), being the result of long-term iatrogenic immunosuppression.

The objective of this study was to review the therapeutic options for resistant PTLD in relation to the new Chimeric antigen receptor-T cell (CAR-T) treatment.

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Treatment Strategies of PTLD

PTLD involves the lymphoid tissue, thus it should be regarded as disseminated disease already at diagnosis, and thus systemic therapy is necessary. Current standard of care includes three strategies of management of EBV infection after HCT: prophylaxis, preemptive therapy, and treatment of proven or probable EBV-PTLD (1). The three major methods of EBV-PTLD therapy include: restoring function of T-cells, reduction of B-cells forming PTLD mass, or targeting the virus (Figure 1).

The classical therapeutic methods used in the prevention, pre-emptive therapy, and treatment of PTLD in the HCT setting include: use of rituximab, immunosuppression reduction (RIS), or administration of EBV-specific cytotoxic T lymphocytes (EBV-CTL) (donor-derived or third-donor party) (1). Other methods, such as donor leukocyte infusion (DLI) and chemotherapy, have nowadays historical value. Additionally, no available antiviral drug is currently effective

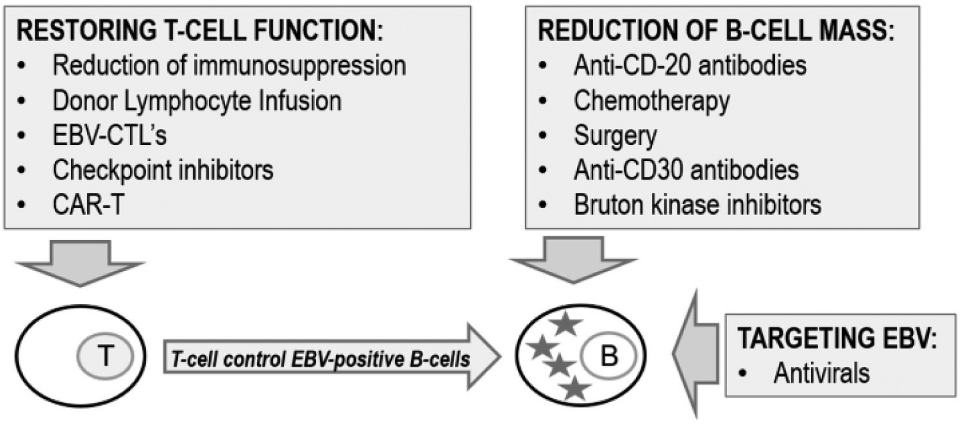

Figure 1. *Three methods of Epstein Barr virus-post-transplant lymphoproliferative disorder (EBV-PTLD) therapy: restoring function of T-lymphocytes, reduction of mass of B-cell lymphoproliferation, and targeting proven/probable EBV. CTL: Cytotoxic T lymphocytes; CAR-T: chimeric antigen receptor-T cell therapy.*

against EBV. This is because EBV does not express activity of thymidylate kinase, which is the target of most antivirals (1). Brincidofovir was shown to have in vitro activity against EBV, but nowadays this drug is no longer available.

Treatment of Established EBV-PTLD

EBV-PTLD, alike NHLs, can grow very quickly, as the EBV duplication time can be as short as ~50 hours. This is why therapy of PTLD should be implemented as soon as possible. Treatment of proven or probable EBV-PTLD is defined as application of therapeutic approach for patients with clinically overt EBV disease. First line therapy of EBV-PTLD includes: (a) rituximab, 375 mg/m^2, usually once weekly; (b) RIS, usually simultaneously with rituximab; and (c) donor-derived or third-party EBV-CTL. Second-line therapy includes: (a) cellular therapy (either DLI or EBV-specific CTLs); (b) chemotherapy with/without rituximab; (c) DLI, obtained from EBV-positive donor. Other methods, such as intravenous immunoglobulins, interferon, and antiviral agents have historical value and are no longer recommended (1).

Results of Therapy of EBV-PTLD

A summary of published real-world data available in the literature shows that for preemptive therapy, the most commonly used method is the application of rituximab with a success rate of 90%. The efficacy of EBV-CTL's is even higher, exceeding 94%; however, this method is available only in selected centers, and the number of patients who have been treated with this approach is lower than two hundred (2). Furthermore, there are no published data on the exclusive use of RIS or DLI in the last decade.

Similar real-world evidence is available for the therapy of EBV-PTLD. Efficacy of exclusive rituximab is at the range of 65%, and in combination with RIS at the range of 78%. RIS is defined as a reduction of ≥20% of the dose of immunosuppressive drugs, except for a low-dose of steroids. Efficacy of EBV-CTLs in the therapy of EBV-PTLD is at the range of 71-75% (2). Again, there are no data from the last decade on the exclusive use of RIS, DLI, chemotherapy or antivirals in the therapy of EBV-PTLD. Moreover, it is rituximab which is used in the vast majority of cases as first-line therapy, and the number of patients treated with EBV-CTL's for EBV-PTLD is low. Still, 22-35% of patients do not respond to first-line therapy with rituximab.

Potential theoretical treatment options considering the various mechanisms of treatment of EBV-PTLD, beyond RIS, rituximab, and chemotherapy include: chemotherapy (usually lymphoma-based regimens), anti-CD20 monoclonal antibodies, DLI, CTLs, histone deacetylase inhibitors, proteasome inhibitors, and checkpoint inhibitors (3).

Therapeutic options involving cellular therapy beyond the standard of care include DLI and CTLs. Cellular therapy either with CTLs or DLI transfers natural EBV-specific cytotoxic T cells to transplant recipient. These cells are active against EBV-infected B-lymphocytes in patients with EBV-PTLD. It was shown that EBV-CTLs were effective in >80% of PTLD patients, thus establishing basic treatment for recipients developing rituximab-resistant PTLD (3).

The standard of care first-line therapy is the use of rituximab (4). Patients who fail first line therapy, should be classified as rituximab-resistant EBV-PTLD. A treatment option for patients with EBV-PTLD post allo-HCT who failed first-line therapy is CTLs. The outcome of this method is very good, but there are limitations related to its availability, the relatively long-term production of CTLs, and

Table I. *Summary of reported cases of therapy of PTLD with CAR-T lymphocytes*.

Source	Number of patients	Age	Type of transplantation	Time to PTLD diagnosis	PTLD first line treatment	CAR-T product	Effect of treatment
Krishnamoorthy *et al*. 2021 (19)	3	M, 54 F, 54 M, 71	Kidney, Pancreas Heart Kidney	20 years 26 years 10 years	1) RIS, Rituximab, chemotherapy 2) RIS, Rituximab, chemotherapy 3) RIS, Rituximab, chemotherapy, ibrutinib	Axi-cel Axi-cel Axi-cel	1) died on day 115 2) died on day 44 3) died on day 15
Yan *et al*. 2021 (20)	2	M, 30 F, 10	HCT HCT	50 days 32 days	1) RIS, Rituximab, chemotherapy 2) RIS, Rituximab, chemotherapy	In-house In-house	1) PTLD resolution, died due to pneumonia 2) alive
Hernani *et al*. 2021 (21)	1	M, 56	Kidney	17 years	Rituximab, chemotherapy	Axi-cel	Alive
Feng *et al*. 2021 (22)	1	M, 46	Kidney	14 years	RIS, Rituximab, chemotherapy	In-house	PR, PTLD relapse and death
Melilli *et al*. 2021 (23)	1	M, 40s	Kidney	18 years	RIS, Rituximab, chemotherapy, auto-HCT	Tisagenlecleucel	PTLD resolution, died for another malignancy
Wang *et al*. 2021 (24)	1	M, 3	Liver	21 months	RIS, Rituximab, chemotherapy	In-house	Alive
Dang *et al*. 2021 (25)	1	F, 17	Heart	4 months	RIS, Rituximab, chemotherapy, radiotherapy	Axi-cel	Alive
Luttwak *et al*. 2021 (26)	3	M, 69 F, 50 M, 66	Kidney Kidney Kidney, Liver	25 years 5 years 8 years	1) Rituximab, chemotherapy 2) Rituximab, chemotherapy, auto-HCT 3) Rituximab, chemotherapy	Tisagenlecleucel Tisagenlecleucel Tisagenlecleucel	1) alive 2) alive 3) alive
de Nattes *et al*. 2022 (27)	1	F, 40	Kidney	5 years	RIS, Rituximab, chemotherapy, auto-HCT	Tisagenlecleucel	PTLD resolution, died due to IPA
Mamlouk *et al*. 2021 (28)	3	M, 38 M, 44 M, 41	Kidney Kidney Kidney	10 years 10 years 7 years	1) RIS, Rituximab, chemotherapy 2) RIS, Rituximab, chemotherapy 3) RIS, Rituximab, chemotherapy, polatuzumab vedotin, bendamustine	Axi-cel Axi-cel Axi-cel	1) Alive 2) PTLD resolution, 3) PTLD resolution

M: Male; F: female; HCT: hematopoietic cell transplantation; Axi-cel: axicabtagene ciloleucel; IPA: invasive pulmonary aspergillosis; PR: partial remission; HCT: hematopoietic cell transplantation.

the cost. The two approaches to overcome limitations related to CTL include a more rapid generation of EBV-specific CTLs, or the generation of third-party EBV-CTLs, which are collected in cell banks and are available for use off-the-shelf, when immediately needed. Data from the last decade show that about 30% of patients present rituximab-resistant forms of EBV-PTLD (3, 5).

After a systematic review of the use of EBV-CTLs for refractory/resistant EBV-PTLD in SOT recipients, eleven studies with 76 patients were identified. Either autologous EBV-CTLs (15/76, 22%) or HLA-matched third-party EBV-CTLs (61/76, 78%) were used. The overall response obtained reached 66% (50/76); complete remission (CR) was achieved in 36/50 and partial remission (PR) in 14/50 patients. In 39/76 patients, EBV viremia was decreased, and no severe adverse reactions were reported (6).

Another option for rituximab-resistant EBV-PTLD is third party off-the-shelf CTLs. The third party EBV-specific CTLs were first tested by Haque et al. in 2007; the best HLA match was the selection criterium (7). Since then, several studies

have shown high safety and efficacy of third party EBV-CTLs in resistant PTLDs. Recently, Prockop et al. described a large allogeneic third-party EBV-CTLs bank, which includes 330 cell therapy products (8). PTLD patients who had failed first-line rituximab treatment were treated with third party CTLs: 68% of HSCT and 54% of SOT recipients demonstrated complete response (CR) or partial response (PR), indicating feasibility of the third-party cell bank.

Possible Future Strategies for the Treatment of PTLD

Out of a number of possible future strategies for the treatment of PTLD (3, 9), the following methods were implemented in real-world practice: anti-PD1 therapy with checkpoint inhibitor nivolumab (10), new anti-CD-20 ofatumumab (11), brentuximab vedotin (12, 13), and zanubrutinib (14). However, for all these innovative methods, only individual cases of successful treatment of rituximab-resistant EBV-PTLD patients have been reported so far.

Chimeric Antigen Receptor T-cells

CAR-T is an innovative method of treatment, based on genetic modification of receptors of T autologous lymphocytes, creating the "living drug" (15, 16). Currently, CAR-T method is used against B-cell malignant lymphoproliferations, such as acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma (NHL), and multiple myeloma (MM) (17, 18). Unexpectedly, this therapy can be potent against resistant EBV-PTLD. This is because EBV-PTLD is a lymphoproliferation of B-lymphocytes, infected with EBV, thus the option of therapy with anti-CD19 CAR-T is justified, especially in rituximab-resistant/refractory (r/r) patients. Clinically, r/r PTLD's have similar biological properties as aggressive lymphomas.

Summary of Reported Cases of CAR-T Treatment of Refractory/relapsed PTLD

Up to August 31, 2022, overall, 10 papers were published (Table I) (19-28), reporting 17 patients, with a median age of 33 years (range=3-71 years); two of them were children. Two patients were post-HCT, and 15 post-SOT, including kidney transplant in 12 patients, and other SOTs in 3 patients. PTLD was developed 32-50 days post-HCT, and 4 months – 25 years (median 10 years) after SOT. In 9 cases, PTLD developed >5 years after SOT. Resistant PTLD was treated with axicabtagene ciloleucel in 8 patients, tisagenlecleucel in 5 cases, and in-house CAR-T product in 4 cases. PTLD resolved in 13 (76.5%) cases; however, 5 patients finally died due to other malignancy (n=3) or pneumonia (n=2). In 4 cases, patients died due to r/rPTLD.

Conclusion

In conclusion, treatment options for patients with refractory EBV-PTLD post HCT who failed first line therapy include: use of EBV-CTL (donor-derived, 3rd party, off-the-shelf), DLI, and chemotherapy, while other methods are in development. The response rate for the use of EBV-specific CTLs for refractory PTLD post-SOT was 66%. The response rate for off-the-shelf allogeneic EBV-CTLs for refractory EBV-PTLD post-HCT was 68%. In real-world case reports, a response to CAR-T treatment for refractory PTLD was observed in 76.5% of patients.

Conflicts of Interest

The Authors declare no conflicts of interest related to this study.

Authors' Contributions

Study design: JS. Data analysis: All Authors. Article writing: JS, JSa, TS. Data check: All Authors. Administrative support: JS. Final approval: All Authors.

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