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REVIEW ARTICLE

VIA MEDICA

Tabelecleucel: a new therapeutic option in refractory EBV-PTLD

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Abstract

Post-transplant lymphoproliferative disorder (PTLD) is classified as an immune-associated lymphoproliferative disease occurring after hematopoietic stem cells transplantation (HCT) or solid organ transplantation (SOT). Rituximab and reduction of immunosuppression are the first line therapy of EBV-DNA-emia and EBV-PTLD and are seen as the 'gold standard' in therapy of post-transplant EBV-related complications. In cases of failed first line therapy with rituximab, regardless of applied reduction of immunosuppression, refractory EBV-PTLD is diagnosed. Refractory EBV-PTLD has a poor outcome, with 2-year overall survival rates of 9.4% and 31.4% following HCT and SOT, respectively, in patients who have failed rituximab and/or chemotherapy. The main treatment options for patients with EBV-PTLD post-HCT who failed first line therapy include the use of EBV-specific cytotoxic T-lymphocytes (EBV-CTLs), which can be donor-derived, third-party donor, or of 'off-the-shelf' origin.

Tabelecleucel is a T-cell product including EBV-specific T-cells originating from a third-party EBV-seropositive donor. These EBV-CTLs were stimulated with B-cells from the same donor, able to recognize B-cells infected with EBV, with no genetic modification used, and expanded in laboratory conditions. Tabelecleucel has been investigated as an ATMP (advanced therapy medicinal product), an on-demand, allogeneic T-cell immunotherapy for the potential treatment of EBV-positive malignancies and diseases. The aim of this narrative review was to assess the third-party donor 'off-the-shelf' cellular product of EBV-CTLs, tabelecleucel, as a therapeutic option of treatment for refractory or relapsing EBV-PTLD.

Key words: hematopoietic cell transplantation, Epstein-Barr virus, post-transplant lymphoproliferative disorder, refractory PTLD, resistant PTLD

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EBV-PTLD

Post-transplant lymphoproliferative disorder (PTLD) is classified as an immune-associated lymphoproliferative disease occurring after hematopoietic stem cells transplantation (HCT) or solid organ transplantation (SOT) [1, 2]. PTLD is defined as uncontrolled neoplastic proliferation of lymphoid or plasmacytic cells after transplantation resulting as a consequence of extrinsic immunosuppression of specific T cells, normally controlling B-cells infected with Epstein-Barr virus (EBV). PTLD belongs to recurrent EBV diseases in a transplant setting, with the incidence of EBV-positivity reaching almost 100% in HCT patients, and c.50% in SOT patients [3].

EBV-PTLD is a rare, acute, and potentially life-threatening hematological malignancy that can occur after

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transplantation when a patient's T-cell immune response is severely suppressed.

EBV-PTLD can be diagnosed at either proven or probable level. Proven EBV-PTLD is confirmed by the detection of EBV-encoded proteins, EBV nucleic acids, or virions in a biopsy-obtained tissue specimen from the affected organ. Probable EBV disease can be diagnosed in the presence of specific EBV-related symptoms (lymphadenopathy, hepatosplenomegaly or other end-organ manifestations), together with significant EBV-DNA-emia, but with no biopsy confirmation from the involved organ [4, 5].

The objective of this narrative review was to assess the third-party donor 'off-the-shelf' cellular product of EBV-specific cytotoxic T-lymphocytes, tabelecleucel, as a therapeutic option for the treatment of refractory or relapsing EBV-PTLD.

Epidemiology of EBV-PTLD

PTLD develops after transplantation when immunosuppressive drugs decrease the number and/or the function of T cells, reducing the natural defense system of the patient. Impaired immunosurveillance can result in failure to adequately control EBV infection, which can lead to persistent EBV viremia, lymphoproliferation, and ultimately EBV lymphomas [6, 7].

It is estimated that the incidence of PTLD after allo-HCT is 1.1–1.7% [8–11], with the number of allo-HCTs performed in EBMT centers estimated to have been 19,796 in 2020 [12]. EBV-PTLD occurs mainly within the first year after the transplant [13], and almost all PTLD cases are EBV-positive [5, 13].

For comparison, the incidence of PTLD after SOT is estimated to be 5–10% [14], depending on many factors, chiefly the type of transplanted organ. The number of SOTs in the EU in 2021 was 26,370 [15], and c.50% of PTLD cases after SOT are EBV-positive [16, 17]. Over 50% of the cases of EBV-PTLD occur more than 12 months post transplant [13].

Treatment strategies of EBV-PTLD

There are three major approaches to EBV infection after HCT: prophylaxis, preemptive therapy, and treatment of established EBV-PTLD. As PTLD is regarded as a disseminated disease at diagnosis with the involvement of lymphoid tissue localized throughout the whole body, only systemic treatment can be applied. The currently available therapeutic approaches applied in the prevention and treatment of EBV-PTLD comprise: the administration of rituximab, reduction of immunosuppression (RIS), and the use of EBV-specific cytotoxic T-lymphocytes (EBV-CTL or VST, viral specific T-cells), which can be of donor origin (including DLI, donor leukocyte infusion), third-party donor, or CAR-T. A further option is chemotherapy, used after SOT rather than after HCT. No antiviral drug is currently effective against EBV, and other methods have only historical value.

Treatment of established EBV-PTLD

Treatment of established EBV-PTLD means therapeutic interventions for patients with probable or proven EBV disease. Therapy of EBV-PTLD should be implemented as soon as possible after a diagnosis is made.

According to ECIL guidelines [5], first line therapy of EBV-PTLD includes: (a) rituximab, 375 mg/m^2, once weekly; (b) RIS, if possible, usually together with administration of rituximab. In cases of rituximab failure, second-line therapy is applied with: (a) adoptive immunotherapy with cellular therapy with *in vitro*-generated donor or third-party EBV-CTL, if available; (b) donor leukocyte infusion (DLI), if available (non-specific cellular therapy, if donor is EBV-seropositive); (c) chemotherapy +/- rituximab. Other methods such as IVIG, interferon and antiviral agents are not recommended as either first or second lines of treatment.

In cases of central nervous system (CNS) involvement, recommended treatment includes: (a) rituximab, either systemic or intrathecal; in the latter case, dose of rituximab to be 10–30 mg in 3–10 mL saline administered weekly; (b) EBV-CTLs; (c) radiotherapy; and (d) chemotherapy ± rituximab according to primary CNS lymphoma protocols based on high dose of methotrexate ± cytarabine [5]. It should be underscored that no standard therapy has been established to date.

Refractory EBV-PTLD

As rituximab is an easily available gold standard of care (SOC) in the therapy of EBV-PTLD in a post-HCT setting, refractory EBV-PTLD can be diagnosed in cases of failure of first line therapy with rituximab, regardless of applied RIS. This can manifest either as a progression of, or stable disease during, treatment with rituximab.

Refractory EBV-PTLD has a poor outcome, with 2-year overall survival (OS) of 9.4% and 31.4% following HCT and SOT, respectively, in patients who have failed rituximab and/or chemotherapy [16, 18], and with median survival of 0.7 months and 4.1 months for HCT and SOT, respectively [16, 18]. For these patients, the standard of care has failed, underscoring the significant need for new therapeutic options.

Therapeutic options for rituximab-resistant EBV-PTLD

Based on possible mechanisms of activity, apart from rituximab and RIS, theoretical treatment options for patients who fail first line treatment (refractory or relapsing

EBV-PTLD; r/r-EBV-PTLD) include: chemotherapy (including classical multi-agent lymphoma-based regimens as well as single agent anti-metabolite therapy); BTK inhibition (ibrutinib); inhibition of PI3K (idelalisib) and mTOR (sirolimus and everolimus); proteasome inhibition (bortezomib); radioimmunotherapy (90Y-ibritumomab tiuxetan); checkpoint inhibitors (pembrolizumab, nivolumab); anti-CD30 therapy (brentuximab vedotin); new anti-CD20 MoAb (obinutuzumab, ofatumumab); sensitization EBV (phenylbutyrate); and cellular therapy (third-donor party CTL, CAR-T, donor lymphocyte infusions) [19–23]. Clinical data shows the successful use of nivolumab, brentuximab, and zanubrutinib in individual cases. In multiple case reports, a response for CAR-T treatment of refractory PTLD was noted in 8/11 patients [24].

Cellular therapy for r/r-EBV-PTLD

The main treatment options for patients with EBV-PTLD post HCT who have failed first line therapy include the use of EBV-CTL (donor-derived, third-party donor, off-the-shelf), DLI and chemotherapy, while other methods are in development.

Nowadays, cellular therapy can be regarded as a basic therapeutic option beyond SOC in HCT setting, and CTLs seem to be the best option. The concept of adoptive cell therapy with EBV-CTLs or DLI is based on the transfer of naturally occurring EBV-specific cytotoxic T cells that can kill EBV-transformed B-cells in recipients with EBV-associated PTLD. It has been shown that adoptive immunotherapy with EBV-CTLs generated from primary HCT donors is an effective approach in the treatment of EBV-PTLD complicating allo-HCT [20]. EBV-specific CTLs have been effective in more than 80% of patients treated for overt PTLD, and have been confirmed in the treatment of transplant recipients with rituximab-refractory PTLD [20].

The use of EBV-CTLs is possibly limited by access to this method, manufacturing facilities, time to generation, and donor availability. Major approaches to circumvent such limitations include the development of techniques allowing the more rapid generation of EBV-CTLs, and the generation of banks of third-party EBV-CTLs which are available for immediate off-the-shelf use [20].

The use of EBV-CTL provides a positive outcome. The response rate (of complete response + partial response (CR+PR) for off-the-shelf EBV-specific T cells for refractory EBV-PTLD post HCT) was 68% [25]. A systematic review of 11 studies including 76 patients with refractory EBV-PTLD after SOT treated with EBV-CTL autologous EBV-CTLs (15/76; 22%) or HLA-matched third-party EBV-CTLs (61/76; 78%) showed the response rate for EBV-CTL treatment to be 66% (50/76). Overall, 36/50 achieved CR and 14/50 achieved PR. EBV-DNA level decreased in 39 patients, and adverse reactions were rare and mild [26].

Third party donor off-the-shelf EBV-CTLs for rituximab-refractory EBV-PTLD

The third-party donor approach was first tested in clinical practice in 2007 by Haque et al. [27], with selection of product based on best HLA match. Over the last 17 years, multiple studies have shown the safety of third party EBV-CTLs, with few adverse events. In 2020, Prockop et al. [25] presented a large third-party donor allogeneic EBV-CTLs bank which included 330 HLA-dependent cell therapy products. First experience in 33 HCT and 13 SOT rituximab-refractory patients showed CR or sustained PR in 68% of HCT and 54% of SOT recipients. This indicates that the third-party bank is feasible and the treatment is safe [28].

Tabelecleucel

Tabelecleucel (Ebvallo™, Atara, Pierre-Fabre Medicament) is a T-cell product including T-cells originating from a third-party EBV-seropositive donor. These T-cells are EBV-specific, after being stimulated with B-cells from the same donor, and are able to recognize B-cells infected with EBV. The cells are expanded in laboratory conditions in order to increase their numbers. Tabelecleucel has been investigated as an on-demand, allogeneic T-cell immunotherapy for the potential treatment of EBV-positive malignancies and diseases. T-cells are specific against EBV, with no genetic modification used (Table I). The product of T-cells is selected and directly delivered from an existing inventory based on an appropriate HLA restriction and a shared allele with the patient [25].

ALLELE phase III study: a new treatment option

Tabelecleucel phase III study (the ALLELE study) data has reported clinically meaningful outcomes and promising objective response rate (ORR) and OS in a population of 43 patients with refractory EBV-PTLD at the level of ORR of 50.0% among all patients, with a best overall response of CR (26.3%; n = 10) or PR (23.7%; n = 9). Median time to response was 1.1 month, but median DOR (duration of response) was not reached. Estimated median OS (mOS) was 18.4 months among all patients. Patients responding to tabelecleucel had a much longer survival compared to non-responders (OS rate at 1 year: 89.2% vs. 32.4%) [29].

In the SOT group, in 15/29 patients a complete or partial response was achieved, and in the HCT group, 7/14 patients. A long-lasting response >6 months was observed in four and six patients respectively after SOT and HCT [29].

Table I. Comparison of CAR-T and VST (viral specific T-lymphocytes)

	CAR-T (tisagenlecleucel, axicabtagene ciloleucel, brexucabtagene autoleucel)	VST (CTL) [Tabelecleucel]
Design of product	Chimeric antigen receptor of T-cells	Stimulated cytotoxic T lymphocytes
Status of product	ATMP (licensed by EMA/FDA)	ATMP (licensed by EMA)
Activity	Monovalent (CD19)	Monovalent (EBV)
Source of cells	Autologous	Off-the-shelf (third-party donor)
Indications	Anti-malignancy treatment: Refractory/resistant ALL/NHL	Antiviral therapy: Refractory EBV-PTLD
Time	3–4 weeks	A few days (off-the-shelf)
Clinical practice	Routine clinical practice	Phase III (therapy)
Adverse effects	Frequent (CRS, ICANS)	Rare (GVHD, hypersensitivity)
Limitations	Obtaining product Cost	HLA restrictions Cost
Other possibilities for development and application	Polyvalent (e.g. CD19/CD22), Other diseases (e.g. myeloma)	Polyvalent (e.g. posoleucel — against: ADV, BKV, CMV, EBV, HHV6, JCV)

ALL — acute lymphoblastic leukemia; ATMP — advanced therapy medicinal products; CRS — cytokine release syndrome; EMA — European Medicines Agency; FDA — US Food and Drug Administration; GVHD — graft-versus-host disease; ICANS — immune effector cell-associated neurotoxicity syndrome; NHL — non-Hodgkin's lymphoma

Additional results of the ALLELE study were as follows:

- Among those eligible to continue after enrollment, 14 had prior HCT, and 29 had SOT.
- Seven of 14 (50%) in the HCT group, and 15 of 29 (52%) in the SOT group, had an objective response, with a median follow-up of 14.1 months and 6.0 months, respectively.
- In the HCT group, the best overall response was CR in 6 (43%), PR in 1 (7%), stable disease (SD) in 3 (21%), progressive disease (PD) in 2 (14%), and not evaluable (NE) in 2 (14%) patients. Median time to response was 1.0 month. Clinical benefit was seen in 10/14 patients (71%). Among the HCT group, estimated 1-year OS was 70.1%, and estimated mOS was not reached.
- In the SOT group, the best overall response was CR in 6 (21%), PR in 9 (31%), SD in 2 (7%), PD in 7 (24%), and NE in 5 (17%). Median time to response was 1.1 months. Clinical benefit was seen in 17/29 (59%) participants. Among the SOT group, estimated 1-year OS was 56.2% and estimated median OS was 16.4 months [29].

In a multicenter expanded access protocol in HCT (n = 14) and SOT (n = 12) recipients treated with tabelecleucel for R/R EBV-PTLD, the overall response rate was 65.4% (including 38.5% with a complete and 26.9% with a partial response): 50.0% in HCT, and 83.3% in SOT. The estimated 2-year OS rate was 70.0%: 61.5% in HCT, and 81.5% in SOT. Patients who responded to tabelecleucel had a much higher 2-year OS rate (94.1%) than non-responders (0%). In general, treatment was well tolerated, with no incidents reported of cytokine release syndrome (CRS), tumor flare, or rejection of transplanted solid organ or marrow [30].

Adverse effects

The most common adverse effects with tabelecleucel, occurring in >10% of patients, include fever, fatigue, rash, decreased appetite, abdominal pain, nausea, diarrhea, constipation, dehydration, hypotension, nasal congestion, anemia, hypoxia, hyponatremia, neutropenia, and increased blood levels of alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase. Severe but rare adverse reactions include tumor flare reaction and graft-versus-host disease (GVHD).

Tabelecleucel, an allogeneic cell therapy, was well tolerated without evidence of the safety concerns typically observed with autologous chimeric antigen receptor cell therapies. More generally,

there have been no reports of tumor flare reaction, infusion reactions, marrow rejection, or CRS, and no evidence for graft-versus-host disease or organ rejection in relation to tabelecleucel [29].

Comparison of efficacy of tabelecleucel to current therapies

In the absence of a control arm, the results of the single-arm phase III ALLELE study were compared to real-world data of 84 patients from the multicenter, multinational RS002 study of patients with EBV-PTLD. Patients in the RS002 study, recruited between 2000 and 2018, had disease relapsed or refractory to rituximab ± chemotherapy and had received the next line of systemic therapy. The use of tabelecleucel was associated with

a substantial OS benefit compared to current treatment, with an unadjusted HR of 0.47 and adjusted HR of 0.37 when using the start of the next line of therapy as the index date [31].

Central nervus system EBV-PTLD

Tabelecleucel has been shown to be effective also in EBV-PTLD with CNS involvement. In analysis of 18 patients with R/R EBV-CNS PTLD (after 0–5 lines of therapy) treated within four open-label studies, the ORR was 77.8%, and 1-year and 2-year OS rates were 70.6% and 54.9%, respectively. There were no treatment-related fatal or life-threatening treatment-emergent adverse events (TEAEs) reported, or serious treatment-related TEAEs of neurotoxicity, organ rejection, GVHD, or tumor flare reaction of any grade [32].

Bank of T-cell lines

The therapeutic approach is based on a dose escalation strategy that has led to the current 3-dose cycle. In the trial, donors to the T-cell bank and recipients shared two HLA alleles. A possible alternative strategy might involve shifting to a different HLA restriction in the subsequent 35-day cycle if patients do not respond to the first one [25].

The *in vivo* expansion approach of the EBV-specific T-cells would allow repeat infusions without CRS or other effects seen in CAR T-cell therapy.

The process of product development has contributed to the lack of adverse events, including those related to HLA incompatibility. The process develops an antigen-presenting cell, essentially a transformed B-cell, that expresses antigens of EBV. These cells were co-cultured with T-cells from the same donor, and the expansion had taken place in an autologous setting. Expansion typically takes up to four weeks, which is much longer than the CAR-T cell process, and there is no artificial activation.

Because the therapy is 'off the shelf,' patients can be treated within 1–2 days from the decision. There is no lymphodepleting chemotherapy used before infusion. The treatment is based on sustained exposure to T-cells without the risk of CRS and other events that could have led to limited doses with other therapies.

Authorization for Ebvallo™ (tabelecleucel)

Based on the results from the pivotal phase III ALLELE study, marketing authorization was granted by the European Commission in December 2022 "under exceptional circumstances" for Ebvallo™ (tabelecleucel) in monotherapy for the treatment of adult and pediatric patients aged >2 years with r/r EBV-PTLD who have received at least one prior therapy. For SOT patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate. Ebvallo™ has demonstrated a favorable risk-benefit profile. Nevertheless, long-term safety and efficacy is still being investigated in ongoing clinical studies.

Tabelecleucel is the first off-the-shelf, allogeneic EBV-CTL immunotherapy approved for the treatment of r/r EBV-PTLD. As EBV-PTLD is a rare disease, Ebvallo™ has 'orphan' designation in Europe; this is reserved for medicines treating rare diseases (those affecting not more than one in 2,000 people). It was reported to be used also in a child case of hydroa vacciniforme-like lymphoproliferative disorder in pediatric common variable immunodeficiency with chronic active Epstein-Barr virus infection [33].

Administration of tabelecleucel

Tabelecleucel is administered intravenously through 5–10 min infusions, and the number of vials per infusion depends on patient weight (2–4 vials per infusion for an adult). It is given over 35-day cycles, and one cycle include infusions on days 1, 8 and 15. The number of cycles to be administered is determined by the response to treatment. If CR or PR is not obtained, patients may be switched to a different lot. Imaging assessment is required around day 28.

Summary

With immunosuppression decreasing normal T-cell response, EBV can multiply, triggering a potentially fatal complication, EBV-PTLD [34], which is a type of lymphoma.

Although it is an uncommon complication, OS with refractory PTLD following HCT remains very challenging [35]. Also, in SOT settings, if patients who develop EBV-PTLD fail to respond to the usual treatment of rituximab ± chemotherapy, survival rates are dismal [20].

Tabelecleucel (Tab-cel), an allogeneic T-cell therapy, which comes 30 years after the discovery that T-cells can be used without the side effects, is a new therapeutic option for r/r EBV-PTLD.

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Authors' contributions
JSt — design of study, analysis of data, writing; MP, JSa, MW — collection of data, writing. All authors — critical revision of paper, final approval.

Conflicts of interest
Nothing to disclose.

Ethics statement

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