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Review article

The biology and treatment of Epstein-Barr virus-positive diffuse large B cell lymphoma, NOS

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ABSTRACT

EBV positive Diffuse Large B-cell lymphoma, not otherwise specified (EBV+DLBCL-NOS) referred to DLBCL with expression of EBV encoded RNA in tumor nucleus. EBV+DLBCL-NOS patients present with more advanced clinical stages and frequent extranodal involvement. Although rituximab-containing immunochemotherapy regimens can significantly improve outcomes in patients with EBV+DLBCL, the best first-line treatment needs to be further explored. Due to the relatively low incidence and regional variation of EBV+DLBCL-NOS, knowledge about this particular subtype of lymphoma remains limited. Some signaling pathways was abnormally activated in EBV+DLBCL-NOS, including NF-κB and JAK/STAT pathways) and other signal transduction pathways. In addition, immune processes such as interferon response, antigen-presenting system and immune checkpoint molecule abnormalities were also observed. Currently, chimeric antigen receptor T-cell (CAR-T) therapy, chemotherapy combined with immunotherapy and novel targeted therapeutic drugs are expected to improve the prognosis of EBV+DLBCL-NOS patients, but more studies are needed to confirm this.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common malignant B-cell lymphoma, accounting for 30%–40% of NHL patients [1]. The etiology and pathogenesis of DLBCL are very complex, and recent studies suggest that the disease spectrum of DLBCL is highly heterogeneous. Epstein-Barr virus (EBV) belongs to the gamma-herpesvirus subfamily and EBVs are spread mainly through saliva, with an insidious infection rate of as high as 90% in the general population [2]. With the decline of immune function, individuals with EBV crypto-infection are at a significantly increased risk of developing EBV-associated malignancies, such as EBV positive DLBCL and Burkitt's lymphoma [3,4] (Fig. 1). EBV positive DLBCL was a distinct subtype of DLBCL and EBV play an important role in this disease [5,6]. Compared with EBV negative DLBCL, EBV positive DLBCL patients present with more aggressive clinical course. In the recent years, NGS sequencing revealed that the molecular features of EBV positive DLBCL were significantly different from EBV negative

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DLBCL, such as gene mutation spectrum and abnormal signaling pathways [7–9]. EBV encoded protein and non-coding RNA (ncRNA) could activate various signal transduction pathways, including NF-κB, phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT), Janus kinase/signal transducer and activator of transcription, JAK/STAT), and lead to lymphoma development [10–12].

No standard regimen has been approved for the first-line treatment in patients with EBV+DLBCL-NOS. The 5-year overall survival (OS) rate was about 25% in EBV+DLBCL-NOS treated by CHOP regimen (cyclophosphamide + doxorubicin + vincristine + prednisone) [4]. Although immune-chemotherapy regimen containing rituximab could significantly improve the survival outcome, the prognosis of EBV+DLBCL-NOS was still worse than that of EBV-DLBCL patients [13]. Recently, new treatment regimens such as HDAC inhibitors, BTK inhibitors and PD-1 inhibitors have been explored in several clinical trials and achieved some encouraging results [14]. However, due to the relatively low incidence of EBV+DLBCL-NOS, knowledge about this distinct subtype was limited. In this review, we summarized the current knowledge on the epidemiology, molecular features, clinicopathological characteristics, treatment and prognostic factors in patients with EBV+DLBCL-NOS.

2. Definition and classification of EBV+DLBCL

In 2003, Oyama et al. firstly reported 22 cases of elderly DLBCL patients with tumor nuclear positive EBV and demonstrated that these patients shared similar clinical features with EBV-associated lymphoproliferative disorders (LPD) [15]. In 2007, Ok et al. further summarized the clinicopathological data of 96 patients and found that, compared with EBV+DLBCL, immunocompetent EBV+DLBCL occurred mainly in elderly males, with a median age of 71 years (range 50–91 years), poor response to treatment and poor prognosis, indicating that elderly patients with EBV+DLBCL were a unique clinical subtype [16].

In 2008, the World Health Organization (WHO) identified monoclonal large B-cell LPD with EBV+ occurring in patients older than 50 years of age without history of immunodeficiency disease or lymphoma as elderly patients with EBV+DLBCL. As EBV+DLBCL could also occur in younger populations, the 2016 WHO revision revised the designation of elderly EBV+DLBCL to refer to not EBV+DLBCL (EBV+DLBCL, not otherwise specified, EBV+DLBCL-NOS) [17].

3. Epidemiology and clinical manifestations of EBV+DLBCL-NOS

The proportion of EBV positive rate in DLBCL is relatively higher (8.7%–11.4%) in Asia and Latin America than in Western countries (<5%) [4]. EBV infection was a risk factor for lymphomagenesis, such as Burkitt lymphoma, NK/T cell lymphoma and EBV+DLBCL-NOS [18,19]. The incidence of EBV+DLBCL-NOS in China accounts for 3.8%–19.0% of DLBCL, and is more common in southern China [20,21]. The different EBV strains and genetic factors (such as human leukocyte antigen type) might partly cause this regional difference.

Most patients with EBV+DLBCL-NOS have high lactate dehydrogenase (LDH) levels, high international prognostic index (IPI) score and poor physical status [4]. EBV+DLBCL-NOS exhibits unique disease characteristics in East Asian populations. EBV+DLBCL-NOS

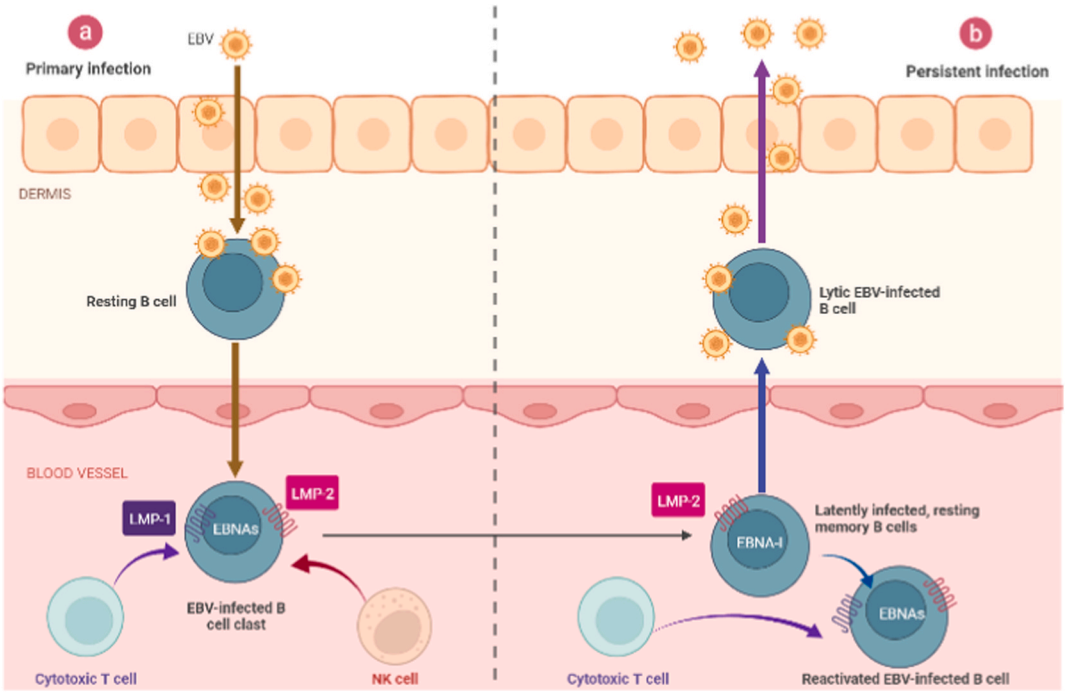

Fig. 1. The process of EBV infection in B cells.

mostly occurs in patients over 50 years of age, but can also occur in young immunocompetent adults, with a male to female ratio of 1.2–3.6:1.0. Most EBV+DLBCL-NOS patients present with advanced stage and extra-nodal involvement [4]. At present, the EBER's diagnostic threshold was undefined. Although the 2016 WHO Classification of Hematologic and lymphoid tumors states that EBER positive in situ hybridization of tumor cells should be >80% [17], the thresholds ranged from 5% to 80% in previous studies [4,22–24].

4. Molecular features of EBV+DLBCL-NOS

Previous studies have demonstrated that EBV oncogene can significantly alter the gene expression of tumor cells and induce chemotherapy resistance. EBV encoded protein and non-coding RNA (ncRNA) could activate a variety of intracellular signal transduction pathways in lymphoma, including B cell receptor pathway (BCR pathway), NF-κB, phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT), Janus kinase/signal transducer and activator of transcription, JAK/STAT) and APC/β-catenin pathway (Fig. 2) [10–12]. For example, latent membrane protein 2A (LMP2A) encoded by EBV can partially simulate B-cell receptor (BCR) signal transduction pathway (Fig. 2) [11], meanwhile, it can also collaborate with MYC oncogene and mutant cyclin D3 to promote cell survival and proliferation [11]. In vitro, LMP1/2A was found to activate Bruton's tyrosine kinase (BTK) pathway in B lymphocytes [11,25]. However, in vivo studies have shown that the expression of LMP1 or LMP2A alone cannot lead to malignant transformation of B cells, and the activity of BTK pathway in EBV+DLBCL-NOS tumor cells is significantly down-regulated [26]. A large number of pathogenic mutations were also detected in EBV+DLBCL-NOS (Table 2) [9,27,28]. For example, Liu et al. analyzed 11 Chinese patients with EBV+DLBCL-NOS using whole exome sequencing [7]. High frequency of pathogenic mutations was detected EBV+DLBCL-NOS, including *LNP1* (11/11), *PRSS3* (10/11), *MUC3A* (9/11), *FADS6* (9/11), and *TRAK1* (8/11) [7].

Next-generation sequencing (NGS) results showed that MYC mutation was the most significant mutation in 9 Chinese EBV+DLBCL-NOS and correlated with prognosis [8]. High frequency mutations in AT-binding domain 1A (45%), lysine methyltransferase 2A/2D (30%), ankevin repeat domain 11 (32%), and Notch homologous 2 (32%) in EBV+DLBCL-NOS tumor cells were found in a recent study [8]. Due to the low incidence of EBV+DLBCL-NOS, the specific incidence of MYC gene rearrangement and "double-hit" lymphoma in patients with EBV+DLBCL-NOS remains unknown.

Another important cause of EBV+DLBCL-NOS is the absence of immune surveillance function due to host immune senescence. In the condition of T cell dysfunction, the LMP1 molecule mimics CD40 co-receptor molecules, leading to rapid and programmed cell proliferation and lymphoma occurrence in B cells, with a large number of programmed death-1 (PD-1) positive lymphocyte infiltration in EBV+LPD [29,30]. It is suggested that immune escape mechanism is involved in the pathogenesis of EBV+LPD. Yoon et al. [31] found that copy number variation and gene expression profile change of molecules related to host immune response in elderly EBV-DLBCL patients were key molecular characteristics that were different from EBV+DLBCL patients. In addition, the expression of PD-L1/2 is high in EBV+DLBCL-NOS patients with low expression of transactivator protein II and major histocompatibility complex II

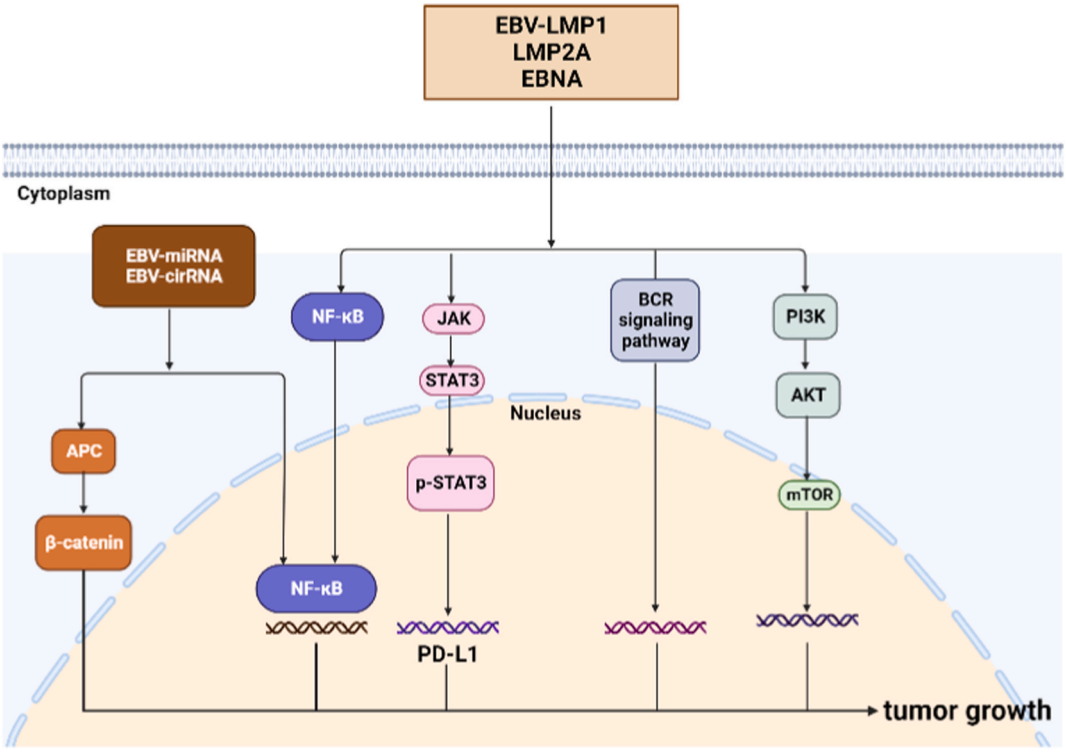

Fig. 2. The signaling pathways activated by EBV in DLBCL.

(MHC II), suggesting that the destruction of antigen-presenting system may also play a role in the pathogenesis of tumor [26].

5. Diagnosis and differential diagnosis

The histopathological features of EBV+DLBCL-NOS patients are atypical. In general morphology, tumor cells may exhibit the characteristics of large cells, central blast cells, immunoblast cells, or Hodgkin-like cells with diffuse distribution or scattered distribution among a large number of reactive background cells [4]. Tumor cells typically express B-cell antigens, including CD19, CD20, CD22, CD79a, and pairing protein 5. In terms of cell origin, 90% of EBV+DLBCL-NOS was non-germinal central subtype, and it was positive for multiple myeloma carcinoma 1 but absent for CD10/B-cell lymphoma 6 (BCL6) [26,32]. In addition, CD30 was detected in about 42% of patients with EBV+DLBCL, however, these patients lack the phenotype of other classical Hodgkin's lymphomas Characteristic [21].

The diagnosis of EBV+DLBCL-NOS includes the exclusion of certain specific types of EBV-associated lymphoma, such as PBL and PEL [4]. The main distinguishing points of clinical and pathological diagnosis include: ① PBL is a highly aggressive lymphoma with a poor prognosis and with a history of immunodeficiency [33,34]; Oral cavity and digestive tract were frequently involved; Pathologically, plasma cell molecular markers were positive without CD20 expression, and the proliferation index is as high as 90%–100%, MYC gene rearrangement was present [34]. ② Most PEL cases have a history of immune deficiency, evidence of HHV-8 virus infection, lymphoma cells often invade the thoracic membrane or pericardial space without forming a significant mass, can express CD45 without expressing B cell molecular markers, and MYC, BCL2 and BCL6 rearrangements are usually negative [4]. ③ The median age of DLBCL-CI patients was about 70 years old, with a history of artificial pneumothorax therapy or chronic inflammatory diseases (such as tuberculosis), but no history of immune deficiency diseases; The masses frequently occurred in the pleura, chest wall or lung adjacent to the pleura, with pain at the corresponding site; TP53 gene mutation and MYC gene amplification were common in lymphoma cells [5].

Around 90% of the EBV+DLBCL-NOS had EBV latency II (LMP11, EBNA22) [35,36]. EBV latency III was frequently observed in the patients with immunodeficiency, such as HIV infection and organ transplantation [37]. Careful evaluation was recommended to identify other factors besides age affecting immunosuppression in patients diagnosed with EBV+DLBCL and latency III [38].

6. Treatment status and prognosis of EBV+DLBCL-NOS

Currently, no standard regimen has been approved for the first-line treatment in patients with EBV+DLBCL-NOS. National Comprehensive Cancer Network (NCCN) do not provide a specific treatment regimen for EBV+DLBCL-NOS patients. As such, the first-line treatment is still referred to the regimen of DLBCL-NOS [4]. The complete response (CR) rate was only 30% and the 5-year overall survival (OS) rate was about 25% in EBV+DLBCL-NOS treated by CHOP regimen (cyclophosphamide + doxorubicin + vincristine + prednisone) [4]. The median OS and the median progression-free survival (PFS) of Chinese patients with EBV+DLBCL-NOS treated with CHOP/R-CHOP ranged from 9 to 37 months and 9.8–20.7 months, respectively [32,39]. The efficacy of immune-chemotherapy in EBV+DLBCL-NOS patients was summarized in Table 1 and rituximab-containing immunochemotherapy could significantly improve the survival rate of EBV+DLBCL-NOS patients [36,40,41], but was still significantly worse than that of EBV-DLBCL patients [13]. Therefore, it is urgent to search novel treatment targets and improve the prognosis in these patients. In addition, due to the relatively low incidence of EBV+DLBCL-NOS and regional distribution differences, knowledge about this particular subtype was limited, multicenter, high-quality prospective clinical studies are lacking, and new treatment options need to be actively explored.

7. New treatment regimens

7.1. BTK inhibitors

In vitro studies have found that malignant transformation of B cells caused by EBV is partly dependent on abnormal activation of BCR/BTK signal transduction pathways, suggesting that BTK inhibitors may be effective agents for patients with EBV+DLBCL-NOS [42]. Latent membrane protein 2A (LMP2A) rewires the downstream intracellular signaling of BCR in EBV-infected B cells and promote

Table 1
A brief summary on the use of immunochemotherapy in patients with EBV+DLBCL.

Study	EBER	Regimen	N	OR/CR rate	OS
Oyama, 2007 [15]	>50%	CHOP	56	80%/66%	5-year: 25%
Ok, 2014 [24]	>10%	R-CHOP	28	89%/NR	5-year: 54%
Lu, 2015 [32]	>20%	R-CHOP	35	66%/NR	3-year: 30%
Zhou, 2019 [8]	>50%	R-CHOP	22	NR	Median: 29.0 months
Witte, 2019 [40]	50%	R-CHOP	60	60%/43%	Median: Not reached
Yoon, 2020 [42]	>20%	I-R-CHOP	24	66.7%/66.7%	Median: 20.9 months
Bourbon, 2021 [36]	>80%	R-chemothrapy	41	73%/73%	Median: Not reached
		Other			
Takahara, 2021 [41]	>80%	R-CHOP	26	71%/50%	3-year: 53%
		Other	22		

Table 2
Major mutations in EBV+DLBCL, NOS.

Study	Major mutations
Liu et al. [7]	LNP1 (11/11), PRSS3 (10/11), MUC3A (9/11), FADS6 (9/11), and TRAK1 (8/11)
Zhou et al. [8]	MYC (3/9), RHOA (3/9), PIM1 (2/9), MEF2B (2/9), MYD88 (2/9), and CD79B (2/9)
Gebauer et al. [9]	ARID1A (21/47), KMT2A (15/47), ANKRD11 (15/47), NOTCH2 (15/47), and KMT2D (14/47)
Cho et al. [28]	PCLO (14/34), TET2 (10/34), LILRB1 (10/34), and SETBP1 (9/34)

oncogenic transformation [11]. Epstein-Barr virus (EBV)-encoded nuclear antigen, EBNA2 could increase CCL3/CCL4 and activate the BTK pathway, resulting in doxorubicin resistance in B cell lymphoma [5]. A Phase II study from Korea explored the efficacy and safety of the BTK inhibitor ibrutinib in combination with R-CHOP in the treatment of EBV+DLBCL, but showed an overall objective response rate of 66.7% in the combination of ibrutinib and R-CHOP (I-RCHOP) group [42]. Although I-RCHOP showed a higher rate of CR than R-CHOP in the subgroup <65 years (87.3% vs. 68.8%), the difference was not statistically significant (P = 0.53). In addition, I-RCHOP significantly increased the rate of treatment-related death compared with R-CHOP in the age ≥65 subgroup, with four patients presenting with unusual infection without grade 3 to 4 granulocytopenia. Given the negative results of this study, it is urgent to explore new target and corresponding new agents in EBV+DLBCL.

7.2. Histone deacetylases (HDAC) inhibitors

As replication of EBVs is independent of thymidin kinase, the conventional antiviral drugs could not inhibit the viral replication as it produced anti-cancer effect on thymidine kinase inhibition [43]. Our previous studies demonstrated that HDAC6 was a potent promoter of lymphomagenesis and HDAC6 inhibitors might be a promising treatment strategy for DLBCL [44,45]. Conventional antiviral drugs combined with HDAC inhibitors exerted a synergistic anti-tumor efficacy. A phase I/II clinical study explored HDAC-active arginine butyrate combined with ganciclovir in 15 patients with relapsed EBV+DLBCL achieved good results, including 4 patients with CR [43]. In addition, HDAC inhibitors may produce cytotoxic effects by decreasing the expression of LMP1 and c-MYC in EBV+ cell lines [46]. A Phase II clinical trial reported that six patients with refractory EBV+DLBCL-NOS treated orally with Vorinostat combined with ganciclovir and achieved an overall response rate (ORR) of 66% and CR rate of 33% [43]. Patients with EBV+ human immunodeficiency virus (HIV)-associated DLBCL had a worse prognosis and rapid disease progression. In 2018, a phase I/II clinical study (AMC-075) completed in the United States explored the safety and efficacy of Vlinoat in combination with R-EPOCH in the treatment of highly aggressive HIV-associated DLBCL patients, and found that one patient with EBV+ HIV-associated DLBCL achieved long-lasting CR, and one HIV-associated DLBCL patient with EBV+ HHV-8+ achieved partial response (PR) after 4 cycles of treatment [47]. However, as the number of cases included in most clinical studies is too small, more clinical studies are needed to confirm the efficacy and safety of the combination regimen of HDAC inhibitors in EBV+DLBCL-NOS patients.

7.3. Immune checkpoint inhibitors

Our previous studies showed that the positive rate of PD-L1 expression was much higher in EBV+DLBCL than DLBCL, NOS [48–50]. The expression rate of PD-L1 was only 8.0%–11.0% in DLBCL-NOS patients, while the expression rate of PD-L1 in tumor cells and tumor microenvironment in EBV+DLBCL-NOS patients was as high as 40.0%–100.0% [48–50]. In DLBCL, PD-L1 expression was associated with EBER positive rate, non-germinal center origin subtypes, and poor prognosis [49]. In EBV+DLBCL, PD-L1+ tumor cells and low-reacting PD1+ TILs were associated with poor clinical outcome [51]. Therefore, PD-1 inhibitor containing regimen might be a promising treatment method in EBV+DLBCL-NOS patients. Although the ORR of PD-1 monoclonal antibody is only about 10% in relapsed/refractory DLBCL patients, PD-1 monoclonal antibody combined with chemotherapy might achieve a better response in first-line treatment of DLBCL patients. In 2019, Younes et al. used Atrilizumab in combination with R-CHOP in 42 DLBCL patients as first-line treatment, the results showed that among 40 DLBCL patients who received atrilizumab, CR rates and PR rates were 77.5% and 10%, and the 2-year PFS and OS rates were 74.9% and 86.4%, respectively [52]. Although adverse events led to treatment termination

Table 3
Summary of clinical trials on first-line treatment of lymphoma patients with PD-1 antibody.

Registration Number	PD-1 antibody	Regimen	Study start date	Study Type	Patients
NCT03258567	Nivolumab	–	2018.04.26	Phase II	EBV^{+}PLD/NHL
NCT03990961	Pembrolizumab	–	2019.09.04	Phase II	PD-L1^{+}DLBCL
NCT03749018	Nivolumab	DA-EPOCH-R	2019.01.02	Phase II	High-grade BCL
NCT03892044	Nivolumab	Duvelisib	2019.11.05	Phase I	Richter syndrom/transformed DLBCL
NCT04181489	Sintilimab	R-CHOP	2019.01.01	Phase II	EBV^{+} DLBCL-NOS
NCT04023916	Sintilimab	R-CHOP	2019.12.01	Phase II	PD-L1^{+} and *TP*53^{mut} DLBCL
NCT04058470	Toripalimab	R-CHOP	2020.04.24	Phase Ib/II	DLBCL/FL3b/EBV+DLBCL ALK+ALCL of the elderly
NCT04476459	Camrelizumab	Apatinib	2020.7.23	Phase I/II	Refractory and Relapsed DLBCL
NCT04796857	Tislelizumab	Lenalidomide	2021.3.31	Phase I/II	Refractory and Relapsed non-GCB DLBCL
NCT04058470	Toripalimab	R-CHOP	2020.4.24	Phase Ib/II	Elderly patients with DLBCL

in 15 patients (36%), consisting mainly of 3 neutropenia, 3 lipase elevations, and 2 amylase elevations, the adverse events were generally manageable, reversible, and the efficacy was sustained. In 2020, Smith et al. [53] treated 30 DLBCL patients with Pembrolizumab combined with R-CHOP in first-line treatment, resulting in 90% ORR and 77% CR rates, and 2-year PFS and OS rates of 83% and 84%, respectively. In this study, 2 patients with high expression of PD-L1 (>50%) in EBV+DLBCL obtained CR after first-line treatment and remained remission. Due to lack of randomized controlled clinical trials, the efficacy of immune checkpoint inhibitors in EBV+DLBCL-NOS needs further investigation. Currently, the favorable safety and potential efficacy of PD-1 monoclonal antibody in the treatment of lymphoma have attracted the attention of many clinicians around the world. A number of clinical studies using targeted PD-1 monoclonal antibody combined with chemotherapy in EBV+ B cell lymphoma patients are in clinical trials (Table 3).

7.4. Other therapeutic approaches under exploration

7.4.1. Cell therapy

Chimeric antigen receptor T-cell (CAR-T) therapy targeting LMP-1 has proved to be effective in nasopharyngeal carcinoma and may be used in EBV+DLBCL patients in the future [54]. Bollard et al. used adenovirus transfected dendritic cells with overexpression of LMP gene to induce and amplify LMP-1/2 specific cytotoxic T lymphocytes in 50 patients with EBV+ lymphoma in vitro, producing an overall response rate of 64% [55]. Recently, a refractory EBV positive DLBCL patient with secondary hemophagocytic syndrome obtained complete remission after receiving sequential combination of PD-1 blockade and CAR-T therapy, opening a new therapy avenue for this entity [14]. However, the investigation of CAR-T therapy in EBV+DLBCL is still in its infancy and need more prospective studies in the future.

7.4.2. Anti-proteasome drugs

EBV+DLBCL is mostly the activated B-cell (ABC) subtype, and the proteasome inhibitor Bortezomib could induce apoptosis of EBV+ B cells. Bortezomib containing therapy attenuated drug resistance via inhibiting NF-κB activity in EBV-infected H929 cells and might be effective in EBV-infected hematologic cancer [56]. However, bortezomib combined with immune-chemotherapy did not produce satisfactory clinical results in patients with ABC subtype DLBCL [57].

7.4.3. PI3K and mTOR inhibitor

As EBV-encoded proteins could activate the PI3K/AKT signal transduction pathway in tumor cells, the PI3K kinase pathway may be a potential treatment target in the future [10]. Sang et al. found that blocking of PI3K/AKT/mTOR pathway in a mouse model inhibited post-transplantation EBV+ lymphoma and prolonged animal survival [58]. In addition, Wang et al. found that mTOR inhibitor lignans B abrogates EBV lytic replication by targeting mTORC2-PKC/AKT-signaling pathway and may be a promising therapeutic option for EBV+LPD [59].

7.4.4. EBV prophylactic vaccine

Epstein-Barr virus (EBV) is the causative pathogen for many kinds of malignancies including several lymphomas such as Burkitt's lymphoma and NK/T cell lymphoma. Although EBV prophylactic vaccines was developed and demonstrated to be effective in preventing EBV infection in mouse model [60–63], no available prophylactic vaccine was launched to the market for clinical use to date. A group from China developed a novel vaccine candidate and designed chimeric virus-like particles (VLPs) based on the hepatitis B core antigen (HBc149) [60]. VLPs elicited neutralizing antibodies in immunized mice, which efficiently blocked EBV infection in cell culture, which offer a robust basis for the development of peptide-based candidate vaccines against EBV [60].

7.5. Other target

CD30 was highly expressed in EBV+DLBCL and was identified as an important prognostic factor [4,21]. Therefore, Vebutuximab may also be potential therapeutic drugs. Two clinical studies evaluating the efficacy of Vibutoxib (and combined with R) in patients with EBV+DLBCL (NCT01671813) were aborted due to lack of research fund. In addition, the ligand for the receptor NKG2D (natural killer group 2D), Retinoic acid early Inducer Protein 1, was highly expressed in EBV+B cells. Animal study have demonstrated that therapy could inhibit EBV+B cell proliferation, however, the effectiveness of targeted NKG2D in humans should be further confirmed in the future [29].

8. Risk stratification and prognostic factors

Previous studies have demonstrated that the prognosis of patients with EBV+DLBCL was worse than EBV-negative DLBCL and EBER positivity was an adverse prognostic factor for DLBCL [36]. Although high level of EBV viral load was an adverse prognostic factor in EBV associated lymphoma, such as Burkitt lymphoma and Hodgkin lymphoma [64,65], the prognostic role of EBV viral load in EBV+DLBCL remains unclear.

Previous studies have shown that the prognosis of young patients with EBV+DLBCL was better than older patients. The International Prognostic Index (IPI) score is a prognostic model commonly used for risk stratification in DLBCL. However, the IPI score is limited in predicting the prognosis of EBV+DLBCL-NOS patients. Prior to rituximab's clinical use, age (≥70 years) and B symptoms were considered to be two independent risk factors for EBV+DLBCL-NOS patients, with median OS of 56, 25, and 9 months for patients with 0 (low risk), 1 (medium risk), and 2 (high risk) independent risk factors, respectively [66]. The difference was statistically

significant ($P < 0.05$). In a smaller study, Beltran et al. showed that higher IPI and higher Oyama scores were associated with worse prognosis in patients with EBV+DLBCL [22]. In addition, lymphocyte count $<1.0 \times 10^9$/L, CD30 and survivin were also associated with poor prognosis of patients [22–24]. In addition, patients with monomorphic pattern had a trend toward worse survival outcome than those with polymorphic cases [36]. Presence of an HLH (hemophagocytic lymphohistiocytosis) was also a key prognostic factor for EBV+DLBCL, NOS [36]. Due to the rarity of this disease, more accurate prognostic model is needed to build based on larger and multicenter study.

9. Perspectives and conclusion

Currently, the pathogenesis, molecular characteristics, treatment response and prognostic pattern of patients remain largely unknown. It is urgent to further explore the biological characteristics and mor effective targeted therapeutic agents. However, the activation of PD-1/PD-L1/2 signal transduction pathway in EBV+DLBCL-NOS is involved in the development of the disease, which provides a good theoretical basis for the exploration of PD1/PD-L1 inhibitors. In addition, cell therapy targeting EBV-encoded proteins is expected to significantly improve survival in patients with EBV+DLBCL-NOS.

Data availability statement

Data included in article/supplementary material/referenced in article.

CRediT authorship contribution statement

Ji-Wei Li: Methodology, Investigation, Formal analysis. **Chao Deng:** Writing – original draft, Validation, Investigation. **Xiao-Yan Zhou:** Writing – review & editing. **Renfang Deng:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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