Diagnostic Pathology

CASE REPORT

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Post-transplant lymphoproliferative disorders after allogeneic hematopoietic stem cell transplantation: a case report, meta-analysis, and systematic review

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Abstract

Background Post-transplant lymphoproliferative disorders (PTLD) are rare but severe complications that occur after solid organ or allogeneic hematopoietic stem cell transplantations (allo-HSCT), with rapid progression and high mortality. Primary central nervous system (CNS)-PTLD are rarely recognized histo-pathologically. In addition, the diagnostic value of the Epstein–Barr virus (EBV) DNA copies in CNS-PTLD remains poorly understood.

Objectives We herein report a case of monomorphic EBV-associated CNS-PTLD (diffuse large B-cell lymphoma, DLBCL) after allo-HSCT and perform a meta-analysis to assess the efficacy of PTLD treatment strategies in recent years.

Methods We present the case report covering clinical manifestations, diagnosis, treatment, and outcomes of a patient with primary CNS-PTLD. Additionally, we include a systematic review and meta-analysis of the clinical characteristics of 431 patients with PTLD after allo-HSCT. We evaluate the main treatment options and outcomes of PTLD management, including rituximab, chemotherapies, and autologous or human leukocyte antigen (HLA)-matched EBV-specific cytotoxic T lymphocyte infusion (EBV-CTLs)/donor lymphocyte infusion (DLI).

Results The meta-analysis revealed an overall response rate of 69.0% for rituximab alone (95% CI: 0.47–0.84), 45.0% for rituximab plus chemotherapies (95% CI: 0.15–0.80), and 91.0% for rituximab plus EBV-CTLs/DLI (95% CI: 0.83–0.96). The complete response (CR) rate after treatments for PTLD was 67.0% (95% CI: 0.56–0.77). Moreover, the 6-month and 1-year overall survival (OS) rate was 64.0% (95% CI: 0.31–0.87) and 49.0% (95% CI: 0.31–0.68), respectively.

Conclusions This case highlighted the urgent need for effective, low-toxic treatment regimens for CNS-PTLD. Our meta-analysis suggested that rituximab combined with EBV-CTLs/DLI could be a favorable strategy for the management of PTLD after allo-HSCT.

Keywords Post-transplant lymphoproliferative disorders, Allogeneic hematopoietic stem cell transplantation, Central nervous system, Rituximab, Meta-analysis

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Introduction

Post-transplant lymphoproliferative disorder (PTLD) is a life-threatening complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT), with variable mortality rates ranging from 7 to 72% [1–3]. Compared with PTLD following solid organ transplantation, PTLD after allo-HSCT tends to be more aggressive, usually characterized by early dissemination and high mortality [4]. PTLD after allo-HSCT is mostly associated with EBV reactivation in donor-derived B cells [5, 6], frequently involved extra-nodal tissues. PTLD isolated to the central nervous system (CNS) is extremely rare [7].

CNS-PTLD mostly occurs within 5 years after transplantation. The incidence of CNS-PTLD varies from 5 to 20% after solid organ transplantation, but it is rarely reported after allo-HSCT [8]. Few cases of primary CNS-PTLD have been reported, mostly following solid organ transplantation. Treatment options for CNS-PTLD include reduction of immunosuppressive agents and rituximab-based therapies. Additionally, whole-brain radiation can also be used [9]. There is still a lack of systemic evaluation of the treatments for PTLD after allo-HSCT.

Herein, we present a case of EBV-associated primary CNS-PTLD after allo-HSCT, detailing the clinical manifestations, neuroimaging, pathological diagnosis, and treatment regimens. Moreover, we conducted a systematic review and meta-analysis to summarize the variable clinical characteristics and treatment outcomes of PTLD after allo-HSCT.

Case presentation

In December 2020, a 45-year-old man presenting with lower limb petechiae and fatigue was admitted to Qilu Hospital, Shandong University, China. He had a history of type 2 diabetes mellitus and fatty liver. The results of peripheral blood, bone marrow (BM) aspirate, and trephine biopsy met the diagnostic criteria for myelodysplastic syndrome (MDS) with excess blasts type 2 (MDS-EB2). Cytogenetic evaluation showed a normal karyotype. Next-generation sequencing identified the ZRSR2 mutation with a variant allele frequency of 16.76%. ZRSR2 mutation is detected in approximately 5% of MDS patients, predominantly in males, and is associated with an elevated percentage of bone marrow blasts and poor prognosis [10]. The revised international prognostic scoring system (IPSS-R) score was very high risk at 7 points.

After 5 cycles of azacytidine (75 mg/m^2/day×7 days), the patient received allo-HSCT from his human leukocyte antigen (HLA)-haploidentical daughter on July 2, 2021. Cyclosporin A (CsA), methotrexate (MTX), and mycophenolate mofetil (MMF) were used as graft-versus-host-disease (GVHD) prophylaxis. BM examination 1 month after the transplantation indicated that the patient achieved complete response (CR) with negative measurable residual disease (MRD) by flow cytometric analysis. Chromosome and short tandem repeat (STR) analysis showed complete donor chimerism. The patient developed grade II acute intestinal GVHD and cytomegalovirus (CMV) viremia. He was then treated with methylprednisolone and recombinant humanized anti-CD25 monoclonal antibody (mAb) at a dose of 1 mg/kg. The patient's intestinal GVHD achieved CR after 3 doses of anti-CD25 mAb infusions. CMV viremia became negative after being treated with ganciclovir, foscarnet sodium, and CMV-specific immunoglobulin. Late-onset grade III hemorrhagic cystitis (HC) occurred on day 46 after transplantation, with BK virus and JC virus positive. The patient had a sudden, convulsive seizure for a few minutes during hyperbaric oxygen therapy for HC, which was resolved spontaneously. Subsequently, he gradually developed slurred speech and bucking. Cranial CT showed a right frontal lobe mass lesion with peripheral edema and multiple ischemic lesions. Magnetic resonance enhancement imaging (MRI) of the brain revealed right frontal gyrus swelling, cortical thickening, and subcortical vasogenic edema (Fig. 1,A and B). Cerebrospinal fluid (CSF) examination by lumbar puncture revealed elevated levels of lymphocytes (7.04×10^6/L). The patient had EBV copies (9.66×10^3 copies/ml) in the mononuclear cells before transplantation, and he developed EBV viremia (2.11×10^2 copies/ml) after the convulsive seizure. The patient then underwent a robot-assisted stereotactic biopsy of the intracranial mass lesion. Pathological examination showed diffusely distributed predominantly large cells with marked perivascular hyperplasia, nuclear fission, and localized necrosis, consistent with histological features of monomorphism. The tumor cells were positive for B-cell markers CD20 and CD79a. In situ hybridization of EBV-encoded RNA (EBER) in biopsy tissues was positive. The immunohistochemical phenotypes were IDH1 (-), GFAP (-), OLig-2 scattered (+), NeuN (-), ATRX scattered (+), Syn (-), Nestin (-), CD20 (+), CD79a (+), CD3 (+), CD5 (+), CD10 (-), MUM-1 (-), Bcl-6 (-), c-Myc (-), Bcl-2 (+), CD30 (2+, 30%), and Ki-67 (+, 60%) (Fig. 1, C-F). IDH1 (-), IDH2 (-), NF1 (-), and STAG2 (-) excluded the diagnosis of glioma. GCET1 (-), CD10 (-), MUM-1 (-), and Bcl-6 (-) indicated a non-germinal center type, confirming the diagnosis of monomorphic PTLD, diffuse large B-cell lymphoma (DLBCL), non-germinal center B-cell type, EBV-positive, which could be categorized as "*Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation*", according to WHO-HAEM5 terminology [11]. We reduced the CsA dosage and administered rituximab

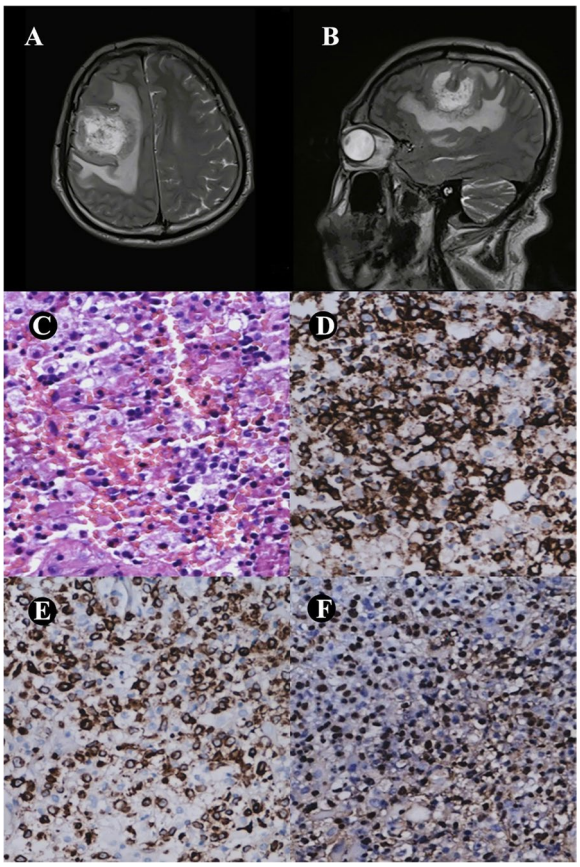

Fig. 1 MRI and histopathological features of CNS-PTLD. (**A** and **B**) Axial and lateral gadolinium-enhanced T2-weighted imaging on MRI. The images showed right frontal gyrus swelling, cortical thickening, and subcortical vasogenic edema. (**C**) Large, atypical cells in the biopsied intracranial mass lesion (H&E stain, ×400). Lymphoma cells were positive for CD20 (**D**), CD79a (**E**), and EBV-encoded small RNA (EBER, **F**) (×400)

at 375 mg/m^2 in combination with methylprednisolone. Despite these approaches, the patient's neurologic symptoms worsened gradually, and he presented with progressive disturbance of consciousness and dyspnea. Eventually, the patient died of pulmonary infection and respiratory failure 6 months after transplantation.

Methods

Literature search

We conducted a comprehensive search of relevant articles in PubMed, Embase, and MEDLINE databases covering the period from 2004 to 2024 on March 24, 2024. The search terms used included: "allogeneic hematopoietic stem cell transplantation", "post-transplant lymphoproliferative disease", and "treatment" or "management". We screened the titles and abstracts of articles for eligibility and reviewed full texts of relevant articles. Moreover, we screened the bibliographies of eligible articles to identify additional studies.

Selection criteria

The criteria for eligible articles were as follows: (1) the article presents original human studies; (2) the article includes patients diagnosed with hematologic malignancies receiving allo-HSCT; (3) the article has to include at least one of the following outcomes: incidence of grade II-IV and III-IV acute GVHD (aGVHD), chronic GVHD (cGVHD), overall survival (OS), relapse incidence, non-relapse mortality (NRM), CMV reactivation, and EBV reactivation. Criteria for exclusion include: (1) the article presents duplicate studies or is a conference report, letter, or without available full text; (2) the article presents only in vitro or animal studies; (3) the article only includes incomplete data or the original data is not available from the authors; (4) the article's original text is not in English.

Data extraction and quality assessment

Data were extracted independently by 2 unblinded authors (Y.Y.S and Y.F.Y), and discrepancies were resolved by discussion. Overall survival (OS), complete response (CR), and partial response (PR) were designated as outcome indicators. If the original study reported survival outcomes using Kaplan–Meier curves, we used the algorithm of Guyot et al. to extract survival data with Engauge Digitizer software [12]. Estimates of 95% confidence intervals (95% CIs) were extracted from the selected studies when available and otherwise were calculated from the reported data. Data extracted from all eligible articles included the first author, year of publication, patient gender, diagnosis, time to PTLD (months), involved sites, histology at diagnosis, CD20 expression, and EBV reactivation (Table 1). Three investigators (Z.Y.Y, J.W.L and F.X.) performed the risk bias assessment for study inclusion independently. Disagreements were resolved by discussion. Cochrane risk-of-bias assessment tool (ROBINS-I) for non-randomized trials was used to assess the risk of bias (Fig. 2).

Statistical analysis

This meta-analysis was performed with R-Project software version 4.2.3 and Review Manager version 5.4. A two-sided P value ≤ 0.05 was considered statistically significant. We graphically displayed the results using the forest plot. Heterogeneity was checked using the chi-square-based Q test and I^2 statistics ($I^2 > 50\%$, $P \leq 0.1$ indicated high heterogeneity). A random-effects model was used for the meta-analysis.

Table 1 Patient characteristics

Study	No. of patients	Gender		Diagnosis								Involved sites		Histology at diagnosis			CD20 positivity		EBV reactivation	
		Male	Female	AML	ALL	MDS	AA	CML	CLL	NHL	MM	Extra-nodal sites	CNS	Early-stage disease	Polymorphic	Monomorphic	(+)	(-)	(+)	(-)
Socié et al.2024	81	49	32	26	13	7	5	4	4	4	0	56	7	2	18	52	52	15	68	3
Lückemeier et al.2023	15	11	4	5	1	1	4	2	0	1	1	–	–	0	1	8	13	2	–	–
Rosello et al.2021	25	13	12	6	3	1	2	7	–	0	2	–	9	–	3	21	19	6	7	2
Salas et al.2020	25	–	–	16	1	3	0	0	0	5	0	–	–	–	–	–	–	–	–	–
Zhu et al.2019	27	19	8	11	9	2	4	0	0	1	0	23	1	–	2	–	8	–	27	0
Jiang et al.2016	84	54	30	39	30	4	9	1	0	1	0	28	10	7	21	0	–	–	–	–
Luo et al.2014	5	3	2	0	2	0	1	0	0	2	–	–	–	1	2	–	–	–	4	–
Styczynski et al.2013	144	–	–	–	–	–	–	–	–	–	–	61	–	–	17	72	77	10	–	–
Chen et al.2013	17	13	4	9	6	1	1	0	0	0	0	–	–	5	5	4	–	–	15	–
Czyzewski et al.2013	8	3	5	2	2	0	2	0	0	0	0	–	8	–	–	–	–	–	8	–
Total	431	165	97	114	67	19	28	18		14	3	168	35	15	69	157	169	33	68	5

AML acute myeloid leukemia, *ALL* acute lymphoblastic leukemia, *MDS* myelodysplastic syndromes, *AA* aplastic anemia, *CML* chronic myeloid leukemia, *CLL* chronic lymphoblastic leukemia, *NHL* non-Hodgkin lymphoma, *MM* multiple myeloma, *DLBCL* diffuse large B cell lymphoma

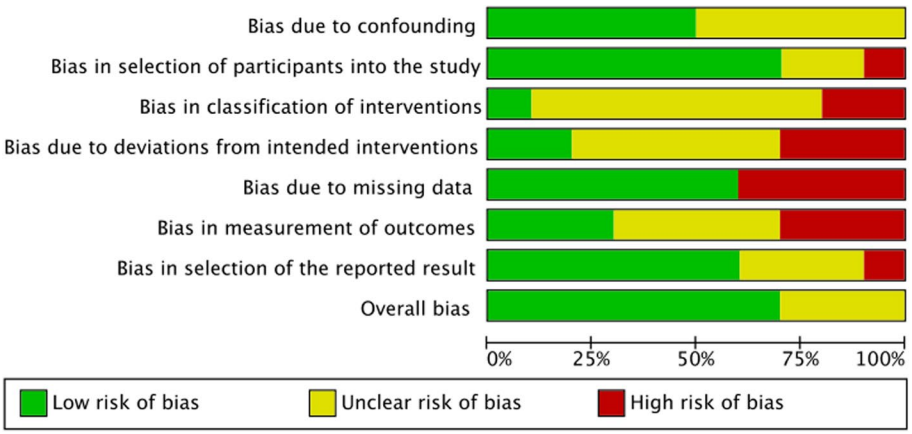

Fig. 2 Risk of bias evaluation maps. We assessed each risk of bias based on the reporting and description of the methodology in the included literature using the revised Cochrane Risk of Bias (ROBINS-I), and used Review Manager software to map the risk of bias evaluation. The quality of the included studies was deemed satisfactory

Results

The search strategy retrieved 297 articles. Among these articles, 41 were reviews, 24 were case reports, and 203 were excluded based on the titles and abstracts. Subsequently, 29 articles were read in detail. After reviewing the full text, we deleted 7 articles with incompatible topics or keywords, 9 articles with incomplete medical record information, and 3 articles with incomplete data that could not be obtained from the authors. Ultimately, 10 articles were included in this pooled analysis. The steps mentioned above concerning the selection of studies are illustrated in Fig. 3.

Study characteristics

The meta-analysis includes 3 single-center studies, 6 multi-center studies, and 1 prospective cohort study [3, 13–21]. Of these studies, a total of 431 PTLD after allo-HSCT patients were enrolled for the analysis of the clinical characteristics data. Patient characteristics are presented in Table 1. Nine studies with 263 patients had detailed information on primary diseases, including acute myeloid leukemia ($n=114$), acute lymphoblastic leukemia ($n=67$), severe aplastic anemia ($n=28$), myelodysplastic syndromes ($n=19$), non-Hodgkin's lymphoma ($n=14$), chronic leukemia ($n=18$), and multiple myeloma ($n=3$). Eight studies with 241 patients provided histologic subtype data. The most common histologic subtype was monomorphic PTLD, which was seen in 157 patients (65.1%), and the rest were polymorphic PTLD (28.6%) and early lesions (6.2%). Among patients with monomorphic PTLD, there were 54 patients with DLBCL, 1 with multiple myeloma (MM), 1 with Burkitt lymphoma, 1 with T-lymphoblastic lymphoma (T-LBL), and 1 with Plasmablastic lymphoma (PBL). CD20 positivity was observed in 169 patients (83.7%). Serum EBV-positive was detected in 68 of the 73 patients (93.2%) with available data.

There were 205 patients with sites of extra-nodal involvement, including the lung, Waldeyer ring, liver, spleen, nasal cavity, and stomach. Thirty-five patients presented with central nervous system involvement, among which 27 patients were clinically diagnosed with primary CNS-PTLD and eight patients with secondary CNS-PTLD. Treatment data was provided for 16 of the 27 primary CNS-PTLD cases. Four patients received high-dose methotrexate at a dose of 3.5 g/m^2, alone ($n=1$) or in combination with additional chemotherapies ($n=3$). Twelve patients received rituximab-based therapy. Eight of the 12 patients received sequential intrathecal rituximab after intravenous failure and achieved CR. One patient did not respond to rituximab-based chemotherapy and was subsequently treated with whole-brain radiotherapy and donor lymphocyte infusion (DLI), achieving CR [14, 17, 19]. Eight patients with secondary CNS-PTLD received intravenous and intrathecal rituximab, among whom 5 achieved CR, 2 achieved PR, and 1 patient died due to clinical progression of PTLD [21]. Although biopsy and pathological examination were the golden standard, the diagnosis of CNS-PTLD in these cases was based on clinical manifestations and imaging without pathological confirmation.

Treatment outcomes

We included 6 studies with 312 patients for the analysis of treatment outcomes of PTLD. The studies enrolled 44 patients receiving rituximab monotherapy, 189 patients receiving rituximab plus chemotherapies, and 79 patients receiving rituximab plus EBV-CTLs/DLI. The overall

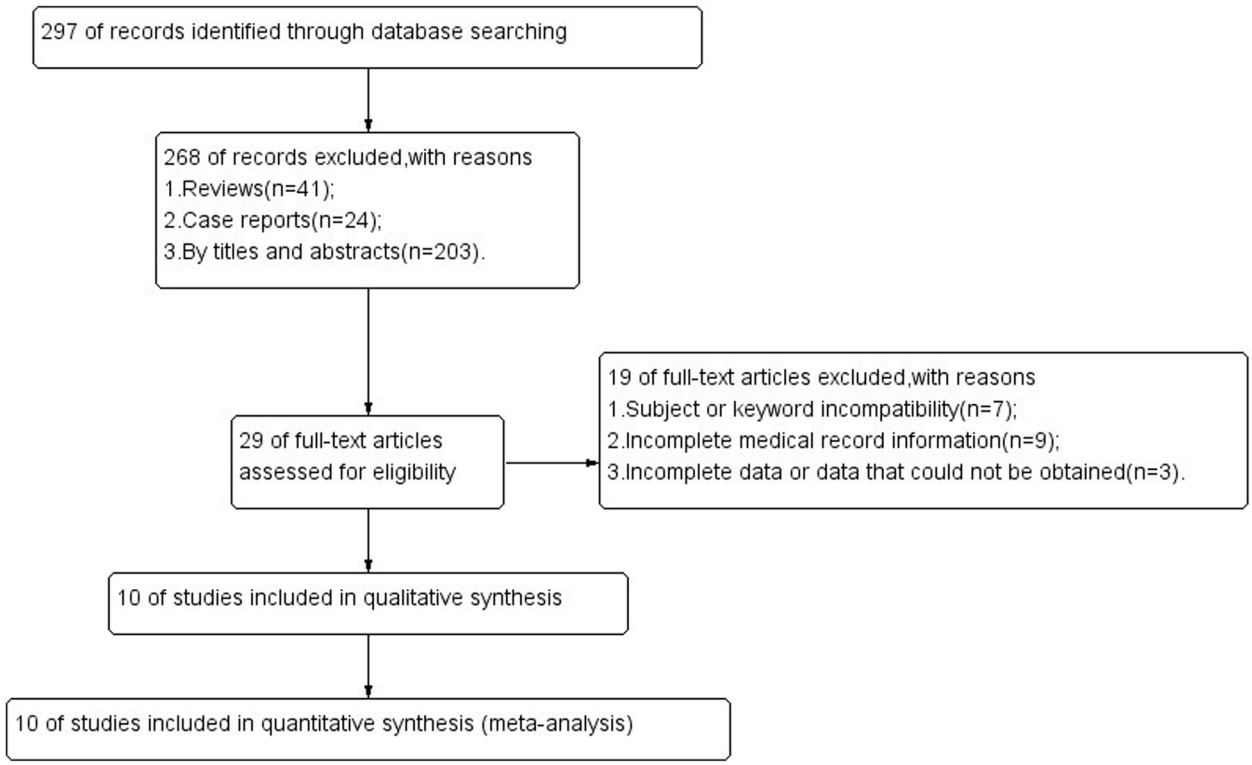

Fig. 3 Stages of the search strategy. The search strategy retrieved 297 articles. Among these articles, 41 were reviews, 24 were case reports, 203 were excluded by the titles and abstracts. A total of 29 articles were read in detail, and 7 articles were deleted due to incompatible topics or keywords, 9 articles due to incomplete medical record information, and 3 articles due to incomplete data that could not be obtained from the authors. Overall, 10 articles were included in the final pooled analysis

response rate (CR + PR) for rituximab, rituximab plus chemotherapies, and rituximab plus EBV-CTLs/DLI was 69.0% (95% CI: 0.47–0.84), 45.0% (95% CI: 0.15-0.80), and 91.0% (95% CI: 0.830.96), respectively (Fig. 4). We included 5 studies of 163 patients with rituximab-based therapy for the analysis of the CR rate. The overall CR rate in these patients was 67.0% (95% CI: 0.56–0.77; Fig. 5). Moreover, the 6-month and 1-year OS rate of 5 included studies with 295 patients was 64.0% (95% CI: 0.31–0.87, Fig. 6A) and 49.0% (95% CI: 0.31–0.68, Fig. 6B). The most common cause of death among these patients was PTLD, followed by GVHD, infections, and other treatment-related deaths. Due to insufficient data, we were unable to stratify the treatment outcomes and survival rates between polymorphic and monomorphic PTLD after allo-HSCT.

Discussion

EBV-associated PTLD is a rare but sometimes fatal complication after allo-HSCT. Major risk factors for PTLD include HLA disparity and T-cell depletion [22]. Currently, published studies on PTLD after allo-HSCT are mostly case reports, case series, and retrospective analyses. There is still a need for a better understanding of the clinical characteristics, treatment strategies, and prognosis of the disease. In the present study, we include the published articles on PTLD after allo-HSCT from the last 2 decades and present a meta-analysis of the clinical characteristics and treatment outcomes of PTLD after allo-HSCT, providing new insights into the management of the disease.

Immunosuppression and EBV activation are major triggers for the development of PTLD [23]. More than 93% of PTLD cases are EBV-positive. For EBV-positive transplant recipients, the oncogenic impact of EBV is the key pathogenic driver of PTLD evolution, while the pathogenesis of PTLD in EBV-negative patients is unclear. Chen et al. found that EBV-negative recipients, being incapable of initiating an EBV-specific cytotoxic T-lymphocyte response, were more susceptible to developing PTLD [24]. Adoptive immunotherapy can stimulate the immune system and induce a robust immune response [25]. Infusions of autologous or HLA-matched EBV-CTLs into transplant recipients with PTLD could induce vigorous EBV-specific cellular immune responses. Therefore, adoptive

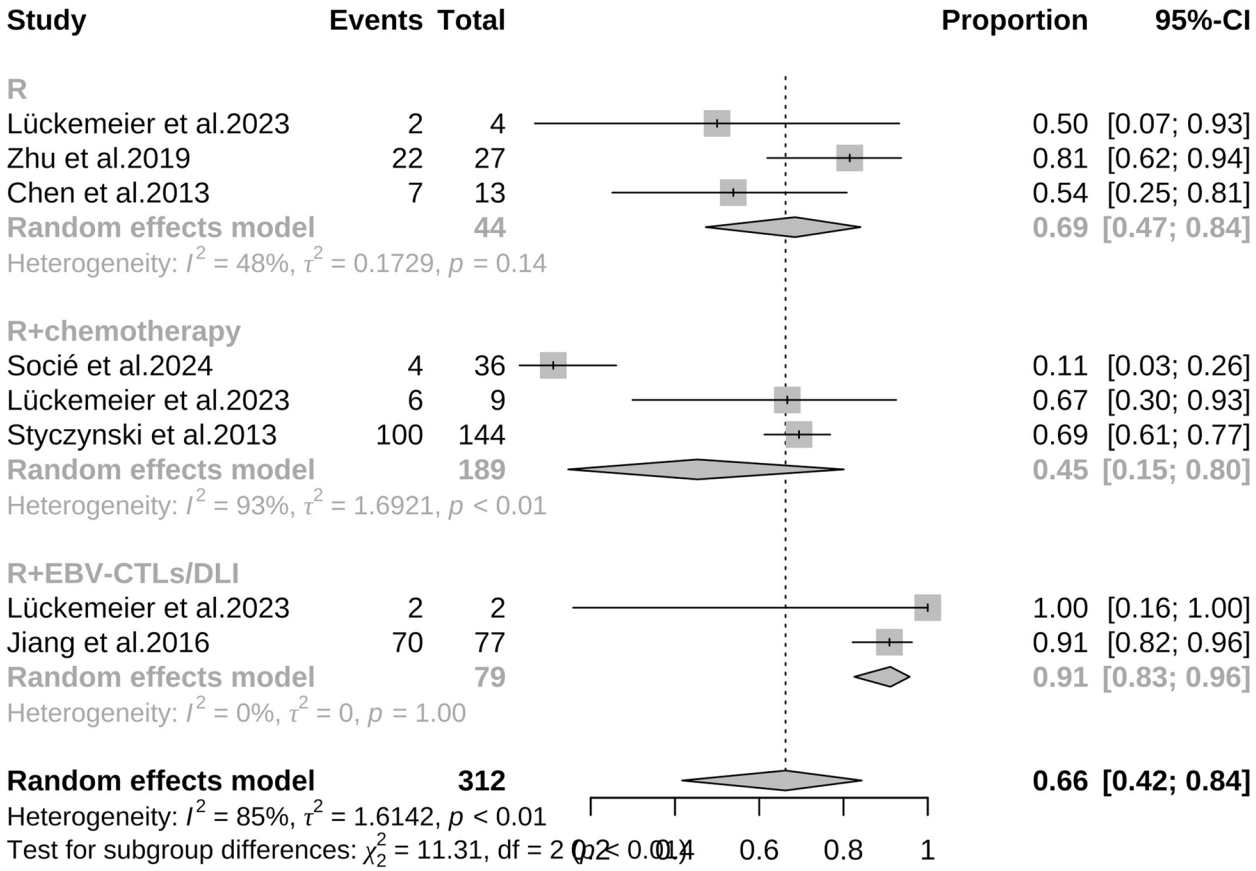

Fig. 4 The overall response of different treatment. In the meta-analysis of the 6 studies enrolled, the overall response rates, including CR and PR, was 69.0% (95% CI: 0.47–0.84) for treatment with rituximab (R), 45.0% (95% CI: 0.150.80) for treatment with rituximab plus chemotherapies (R + chemotherapies), and 91.0% (95% CI: 0.830.96) for rituximab plus EBV-CTLs/DLI (R + EBV-CTLs/DLI). Abbreviations: EBV-CTLs, Epstein-Barr virus-specific cytotoxic T lymphocytes; DLI, donor lymphocyte infusion

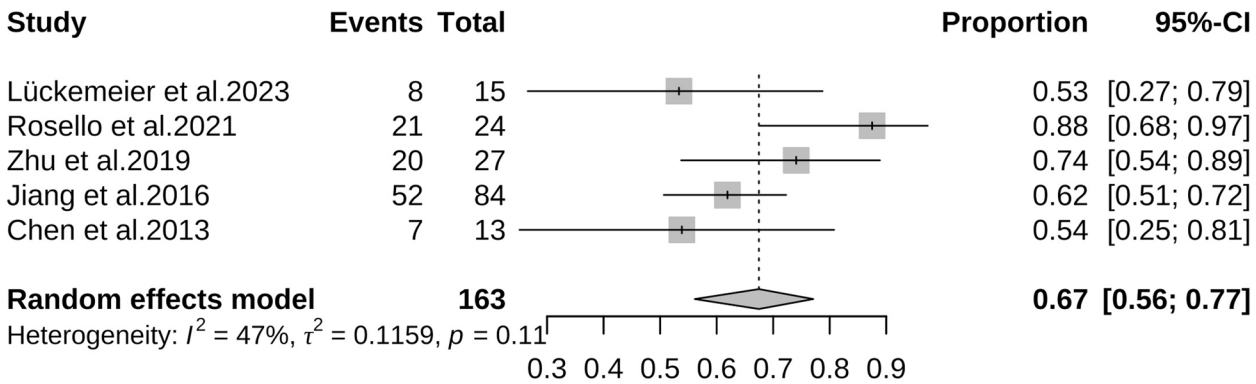

Fig. 5 Complete response of patients. In the meta-analysis of 5 studies with 163 patients, the overall CR rate in the PTLD treatment was 67.0% (95% CI: 0.56–0.77)

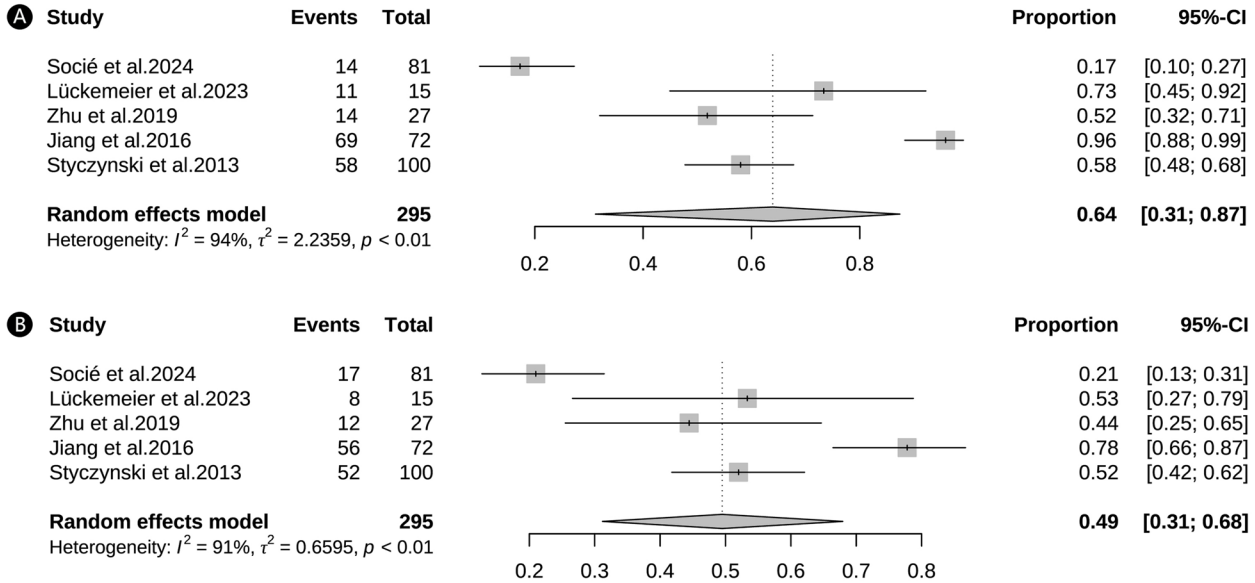

Fig. 6 Six-month and 1-year OS. In the meta-analysis of 5 studies with 295 patients, the 6-month OS rate was 64.0% (**A**, 95% CI: 0.31–0.87), the 1-year OS rate was 49.0% (**B**, 95% CI: 0.31–0.68)

immunotherapy has good potential in the treatment of PTLD [26].

Current guidelines recommend the reduction of immunosuppression (RIS) and rituximab as first-line therapies, and EBV-CTLs, DLI, and chemotherapies as second options for PTLD [27]. RIS is foundational in PTLD treatment, which improves cytotoxic T-cell functions and attenuates abnormal lymphocyte proliferation. However, the optimal dosage for RIS is not well-defined and should be tailored according to patient tolerability, tumor response, and graft functions [28]. More recently, the importance of first-line use of rituximab with or without RIS has been increasingly recognized, with an efficacy of over 60% for EBV-PTLD [29]. In our meta-analysis of the 5 studies, 66.0% of the patients treated with rituximab-based therapy achieved CR, suggesting that rituximab was an effective therapeutic option for PTLD. Trappe et al. showed that sequential first-line treatment with rituximab followed by cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) was more effective than initial rituximab monotherapy followed by chemotherapy upon progression or relapse [30]. For patients who failed the first-line therapies, second-line options such as chemotherapies, EBV-CTLs/DLI, surgical resection, and localized radiotherapy can be considered [24]. Our analysis indicated that sequential first-line treatment with rituximab followed by EBV-CTLs/DLI had a higher response rate. Randomized controlled trials comparing the efficacy of these treatments are still needed.

Primary CNS-PTLD after allo-HSCT is extremely rare and barely pathologically recognized through cerebral biopsy. Prognosis varies significantly, with some patients dying within the first month while others surviving for years [28]. Early diagnosis and appropriate intervention are crucial for patient outcomes. In previous case reports, diagnostic practices for CNS-PTLD had primarily relied on imaging and EBV serologic tests, which were insufficient. Brain biopsy remains to be the golden standard and should always be considered in clinical settings to ensure accurate diagnosis and appropriate management [31]. The standard treatment for CNS-PTLD has not been established due to the absence of high-quality evidence. Rituximab is frequently used in the case series for CNS-PTLD. Zimmermann et al. demonstrated that the combination of whole-brain radiotherapy (WBRT) and rituximab was an effective treatment [32]. We reported a case of primary CNS-PTLD after allo-HSCT, which was diagnosed with DLBCL after histopathological examination via robot-assisted stereotactic biopsy. The patient received early intervention based on RIS and rituximab; however, the CNS-PTLD progressed rapidly, and the patient died 6 months after transplantation.

There were limited studies evaluating the clinical characteristics and treatment outcomes. The degree of inconsistencies in the characteristics reported by these studies made their inclusion very challenging

and added significant heterogeneity to the findings. Although the treatment outcomes of 312 patients were reported, we were unable to compare the efficacies of different treatment options because the vast majority of patients received sequential therapy after failing the initial treatment. Moreover, we were unable to stratify the separate treatment effects or survival rates between polymorphic and monomorphic PTLD due to the lack of data.

There were several risk factors for PTLD in our case, including ATG pretreatment, EBV infection, 6/10 HLA-matched haploidentical donor hematopoietic stem cell graft, and prolonged administration of immunosuppressive agents. After the diagnosis of CNS-PTLD, the patient's overall condition deteriorated, making him intolerant to combined chemotherapies. Although CsA dosage was reduced and rituximab was given, his CNS-PTLD still worsened, leading to severe pulmonary infection and fatal respiratory failure. This case illustrated an urgent need for effective, low-toxic new regimens for the treatment of CNS-PTLD.

Authors' contributions

Y.S. and Y. Y. were involved in Conceptualization, Methodology, Investigation, Formal Analysis, and Writing - Original Draft; Z.Y., J.L., F.X., M. X., and Q. F. were involved in Data Curation, Resources and Supervision; X. J.,X.D., and W.W. were involved in Visualization and Investigation; C.L. and P.J. were involved in Resources and Supervision; X.L. and Y.Z.was involved in Conceptualization, Funding Acquisition, Resources, Supervision and Writing - Review & Editing.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Our study was approved by the ethics committees of Qilu Hospital of Shandong University according to the Helsinki Principles. Written informed consent was obtained from the family members of the patient for the publication of the clinical information.

Competing interests

The authors declare no competing interests.

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