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ORIGINAL RESEARCH

Expert Consensus on the Characteristics of Patients with Epstein–Barr Virus-Positive Post-Transplant Lymphoproliferative Disease (EBV$^+$ PTLD) for Whom Standard-Dose Chemotherapy May be Inappropriate: A Modified Delphi Study

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ABSTRACT

Introduction: Following hematopoietic stem cell transplantation or solid organ transplantation, patients are at risk of developing Epstein–Barr virus-positive post-transplant lymphoproliferative disease (EBV$^+$ PTLD), which is an ultra-rare and potentially lethal hematologic malignancy. Common treatments for EBV$^+$ PTLD include rituximab alone or combined with chemotherapy. Given specific considerations for this population, including severity of the underlying condition requiring transplant, the rigors of the transplant procedure, as well as risks to the transplanted organ, there is a group of patients with EBV$^+$ PTLD for whom chemotherapy may be

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inappropriate; however, there is limited information characterizing these patients. This study aimed to reach expert consensus on the key characteristics of patients for whom chemotherapy may be inappropriate in a real-world setting.
Methods: A two-round modified Delphi study was conducted to reach consensus among clinicians with expertise treating EBV^+ PTLD. Articles identified in a targeted literature review guided the development of round 1 and 2 topics and related statements. The consensus threshold for round 1 statements was 75.0%. If consensus was achieved in round 1, the statement was not discussed further in round 2. The consensus thresholds for round 2 were moderate (62.5–75.0%), strong (87.5%), or complete (100.0%).
Results: The panel was composed of a total of eight clinicians (seven hematologists/hemato-oncologists) from six European countries. The panel generated a final list of 43 consensus recommendations on the following topics: terminology used to describe patients for whom chemotherapy may be inappropriate; demographic characteristics; organ transplant characteristics; comorbidities that preclude the use of chemotherapy; EBV^+ PTLD characteristics; and factors related to treatment-related mortality and morbidity.
Conclusions: This modified Delphi panel successfully achieved consensus on key topics and statements that characterized patients with EBV^+ PTLD for whom chemotherapy may be inappropriate. These recommendations will inform clinicians and aid in the treatment of EBV^+ PTLD.

Keywords: Chemotherapy; Delphi panel; Epstein–Barr virus; Post-transplant lymphoproliferative disease

Key Summary Points

Recipients of allogeneic hematopoietic stem cell transplantation (HCT) or solid organ transplantation (SOT) are at risk of developing Epstein–Barr virus-positive post-transplant lymphoproliferative disease (EBV^+ PTLD), an ultra-rare and potentially lethal hematologic malignancy.

Standard-dose chemotherapy may not be well tolerated by transplant recipients and is associated with excessive toxicity and increased treatment-related mortality.

No clinical guidelines or protocols currently describe the characteristics, risk factors, or recommended treatments for patients with EBV^+ PTLD who may be ineligible for chemotherapy.

The purpose of this modified Delphi panel study was to obtain clinical expert consensus on the characterization of patients with EBV^+ PTLD for whom chemotherapy may be inappropriate.

INTRODUCTION

Post-transplant lymphoproliferative disease (PTLD) is an ultra-rare and aggressive disease that may occur as a result of immunosuppression following allogeneic hematopoietic stem cell transplantation (HCT) or solid organ transplantation (SOT) [1–3]. Nearly all PTLD cases following HCT and 47–68% of PTLD cases following SOT are caused by the Epstein–Barr virus (EBV) [1], which is associated with immune

system dysregulation and B cell hyperproliferation during immunosuppression [1, 3]. EBV-positive (EBV^+) PTLD may occur via primary infection, when patients who are EBV-seronegative receive a transplant from EBV^+ donors, or more frequently, when EBV reactivates in previously infected patients following transplantation [1, 3]. The life-long use of immunosuppressive therapy is a main risk factor for SOT recipients [1].

Treatment options for patients with EBV^+ PTLD following HCT and SOT include reduction of immunosuppression (RI), surgery or radiation therapy in localized disease, rituximab monotherapy or rituximab with chemotherapy, use of antiviral agents, and cellular therapy [4–8]. Although there are no approved treatments by the US Food and Drug Administration or the European Medicines Agency for this disease, treatment guidelines from the American Society of Transplantation [9], British Society of Hematology (BSH) [10], European Conference on Infections in Leukemia (ECIL) [11], and the National Comprehensive Cancer Network (NCCN) [12] recommend the response-stratified sequential use of RI, rituximab, then chemotherapy. In patients with EBV^+ PTLD following HCT, rituximab monotherapy is used as an established initial treatment; however, chemotherapy is usually reserved as a rescue treatment or is avoided completely as it is associated with high treatment-related mortality and poor outcomes [11, 13–15]. Rituximab administered with or without chemotherapy is the recommended therapy in patients with EBV^+ PTLD following SOT [7, 9, 10]. The PTLD-1 trial, which included patients with PTLD following SOT, demonstrated safety and efficacy in the sequential treatment of rituximab followed by cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy [16]. A subsequent trial investigating risk-stratified sequential treatment demonstrated the role of rituximab monotherapy consolidation in patients who demonstrated complete remission following four weekly cycles of rituximab induction. Patients who did not exhibit a complete response after four cycles of rituximab received CHOP concomitantly [17–19].

Recommended treatments for EBV^+ PTLD following transplantation may have treatment-related adverse events. RI can lead to graft-versus-host disease (GvHD) and bone marrow rejection in HCT recipients and rejection of transplanted organs in SOT recipients [1, 2, 11, 13]. Standard-dose chemotherapy is not well tolerated by most HCT and some SOT recipients and is associated with excessive toxicity [6], infectious complications to long-standing immunosuppression in the SOT setting [10, 20], and increased treatment-related mortality in all transplant settings [7, 21, 22]. As a result, many patients will be considered to be ineligible for chemotherapy. Therefore, a challenge in the treatment of EBV^+ PTLD is the balance between minimizing treatment-related toxicity and infection, and maintaining transplanted organ function while aiming to cure PTLD.

Treatment options are limited if patients have EBV^+ PTLD that relapses or is refractory to rituximab and/or chemotherapy [23, 24]. Treatment outcomes in HCT recipients following rituximab treatment failure are usually very poor [25], with a median overall survival (OS) of 0.7 months [24]. Likewise, SOT recipients with EBV^+ PTLD that has relapsed or is refractory to rituximab plus chemotherapy have a reported median OS of 4.1 months [23]. Therefore, urgency is required to identify effective, well-tolerated therapies for patients with EBV^+ PTLD for whom rituximab and/or chemotherapy has failed.

No clinical guidelines or protocols characterize the specific patients with EBV^+ PTLD who may be ineligible for chemotherapy, likely because of the complicated and challenging nature of the condition and the lack of prospective studies on the disease. To address this knowledge gap, the present study used the Delphi method, a structured communication technique that aims to develop consensus among a panel of experts in the presence of limited evidence or when the existing evidence is contradictory within the specific topic of interest. The purpose of this modified Delphi panel study was to obtain clinical expert consensus on the characterization of patients with EBV^+ PTLD for whom chemotherapy may be inappropriate. The recommendations from this

panel may help inform EBV$^+$ PTLD clinical practice and future clinical trial designs.

METHODS

Targeted Literature Review

A targeted literature review was conducted using MEDLINE® via PubMed to identify published practice guidelines, protocols, or epidemiological literature specific to patients with EBV$^+$ PTLD who were unable to receive chemotherapy or for whom chemotherapy may be inappropriate. To retrieve relevant information, results were limited to English language only, human subjects only, and information published within the past 10 years. Identified articles were used to inform topic selection for round 1 discussion, which aimed to achieve consensus on how to characterize the target population. Study procedures are described in Fig. 1.

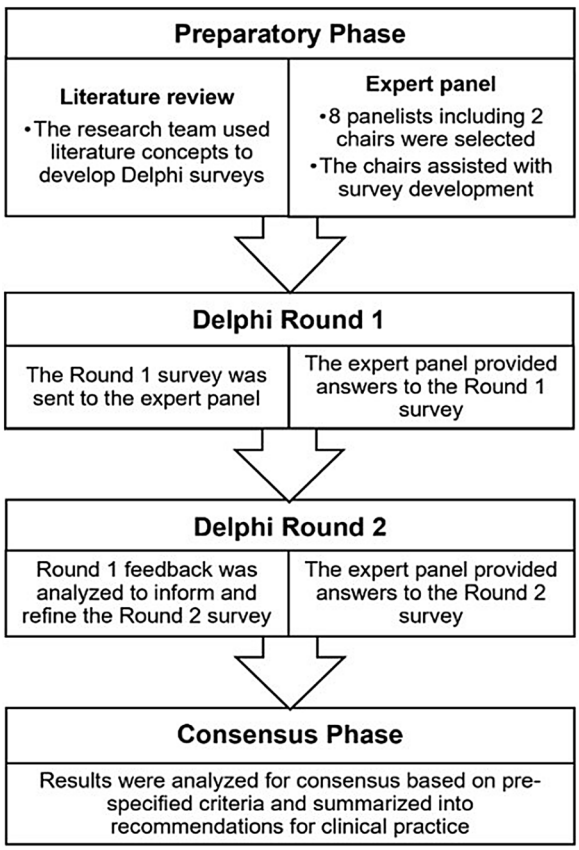

Fig. 1 Flowchart of study procedures

Modified Delphi Panel Process

Study Design and Panel Selection

This study used the modified Delphi method, a two-round structured process that utilizes surveys to reach consensus on complex issues while preserving participant anonymity [26, 27]. The modified Delphi method for this study was developed prior to panel selection and initiation. Eight clinicians with expertise treating EBV$^+$ PTLD served as Delphi panelists. Panelists were invited on the basis of broad geographical representation and their specialty areas, and two experts served as panel chairs and assisted in selecting round 1 topics that would be suitable for wider panel discussion.

Round 1 Survey

The round 1 online survey consisted of 90 statements that focused on terminology and characteristics that describe patients with EBV$^+$ PTLD who were unable to receive chemotherapy or for whom chemotherapy may be inappropriate. The survey included a mixture of open-ended and closed-ended statements that focused on five main topics: (1) terminology to describe the patient population of interest; (2) demographic characteristics; (3) organ transplant characteristics; (4) comorbidities that preclude the use of CHOP; and (5) factors related to chemotherapy-related mortality and morbidity. The results from the round 1 survey helped to determine the statements and wording of response options that were featured in the round 2 survey.

Round 2 Survey

The round 2 online survey consisted of 72 statements that aimed to achieve consensus on the terminology and characteristics that describe patients with EBV$^+$ PTLD for whom chemotherapy may be inappropriate. In this round, the definition of chemotherapy was broadened from CHOP to standard-dose chemotherapy. Four main topics were included: (1) demographic characteristics and (2) organ

transplant characteristics of patients for whom standard-dose chemotherapy is not appropriate; (3) comorbidities that preclude the use of standard-dose chemotherapy; and (4) factors related to chemotherapy-related mortality and morbidity.

Data Analysis

A five-point Likert scale was used in rounds 1 and 2 to assess panelist alignment on closed-ended questions. Likert scale agreement was met if clinicians responded with "agree" or "strongly agree", or "disagree" or "strongly disagree." For open-ended questions, clinician responses were coded using qualitative methods to merge similar concepts and determine consensus.

Consensus thresholds used in this study were established a priori and aligned with those used in previous Delphi panels [27]. The consensus threshold for the round 1 survey was 75.0% of panelist responses. If a statement or concept in round 1 reached this threshold, it was considered to have reached consensus and was not subsequently voted on during round 2. Three consensus thresholds were used for the round 2 survey: moderate (62.5–75.0%), strong (87.5%), or complete (100.0%).

The goal of both surveys was to reach consensus on subtopic statements (e.g., impaired heart function and impaired liver function) within a main topic (e.g., comorbidities that may preclude the use of chemotherapy). Survey data and panelist demographic information were summarized descriptively.

Compliance with Ethics Guidelines

This article is based on a modified Delphi panel study, which collated confidential online survey responses on a specific topic from eight clinicians who served as panelists. Approval from an ethics committee or an internal review board was not required as this study was considered as a consensus development technique and did not involve research on patients. All participating clinicians agreed to serve as panelists, agreed with the modified Delphi panel study objectives, participated in manuscript development, and agreed to the publication of this manuscript.

RESULTS

Publications from Literature Review

Of the 110 abstracts identified via a PubMed MEDLINE® search, 21 articles were selected for full article review, and 15 were selected for in-depth review and analysis based on the inclusion and exclusion criteria. This review yielded limited information on the characterization of patients with EBV^+ PTLD for whom chemotherapy may be inappropriate. Findings and key questions identified in the review were summarized by topic (demographics, organ transplant characteristics, PTLD characteristics, comorbidities that preclude the use of CHOP chemotherapy, and factors related to treatment-related mortality and morbidity) and subtopic (e.g., age or type of organ; Supplementary Material Table S1).

Panelists' Clinical Expertise

Given the rarity of EBV^+ PTLD, panelists were selected from a small pool of clinicians with expertise in the treatment and management of EBV^+ PTLD. Eight clinical experts were invited to serve on the study panel. All panelists participated in and completed round 1 and 2 surveys. The panel was mostly composed of hematologists/hemato-oncologists (n = 7, 87.5%), with all panelists having expertise in treating EBV^+ PTLD. Expertise was based on the number of years treating patients with EBV^+ PTLD (mean [range] 17.1 [5–30]) and the number of patients managed for PTLD in the previous 2 years (mean [range] 21 [10–50]). On average, 42.5% of managed patients with PTLD were EBV^+. Additional information on the panelists' demographic characteristics and clinical expertise can be found in Supplementary Material Table S2.

Table 1 Rounds 1 and 2 Delphi survey topics

Round 1 survey topics	Round 2 survey topics
Terminology to describe the patient population of interest[a]	N/A
Demographic characteristics of patients (e.g., age) for whom chemotherapy is not appropriate	Demographic characteristics of patients for whom standard-dose[b] chemotherapy is not appropriate
Organ transplant characteristics of patients for whom chemotherapy is not appropriate	Organ transplant characteristics of patients for whom standard-dose[b] chemotherapy is not appropriate
EBV^+ PTLD characteristics of patients for whom chemotherapy is not appropriate[a]	N/A
Comorbidities that preclude the use of intensive chemotherapy	Comorbidities that preclude the use of intensive chemotherapy
Factors related to chemotherapy-related mortality and morbidity	Factors related to chemotherapy-related mortality and morbidity

CHOP cyclophosphamide, doxorubicin, vincristine, and prednisone, *EBV^+ PTLD* Epstein–Barr virus-positive post-transplant lymphoproliferative disease, *N/A* not applicable

[a]No follow-up was needed from round 1

[b]Round 1 survey questions specified CHOP, while round 2 was broadened to specify standard-dose chemotherapy

Delphi Panel Survey Results

Survey topics included in rounds 1 and 2 are presented in Table 1. Statements that achieved consensus in round 1 were not discussed further in round 2.

Round 1 Survey Results

Panelists reviewed 42 statements on the following topics: terminology to describe the relevant patient population; age ranges of pediatric, adult, and geriatric patients; socioeconomic demographics; and patient clinical status assessments and characteristics. Overall, 23 (54.8%) statements reached a consensus of at least 75.0%, and 17 statements did not reach consensus.

Terminology and Demographic Characteristics to Describe Target Patients

Panelists agreed that the terms "CHOP-inappropriate" and "CHOP-ineligible" can be used interchangeably to describe patients who receive rituximab treatment, do not achieve a complete response, and those who would not be recommended to receive CHOP chemotherapy (Table 2). Additionally, panelists agreed on the minimum and maximum ages that define pediatric and geriatric patients. Panelists also achieved consensus on specific patient characteristics (e.g., Eastern Cooperative Oncology Group [ECOG] performance and Karnofsky performance criteria) and clinical assessments that should be used to determine chemotherapy treatment eligibility (Table 2).

Round 2 Survey Results

Open-ended responses and subsequent discussion from round 1 generated 70 statements for round 2 review. At this stage, the definition of chemotherapy was broadened from CHOP to standard-dose chemotherapy. These statements aimed to achieve consensus on recommendations regarding patient demographics, organ transplant characteristics, comorbidities, and risk of chemotherapy-related mortality and morbidity. Of the 70 statements generated, 42 (60.0%) reached complete, strong, or moderate consensus, and 28 did not reach consensus.

Patient Demographic and Clinical Characteristics

Two statements regarding patient demographic characteristics achieved moderate or complete

Table 2 Summary of key recommendations for patients with EBV^+ PTLD

Recommendations	Source (Round 1 and/or Round 2)	Panelists who "agree" or "strongly agree" *n* (%)	Consensus rating[a]
Terminology to describe target population			
• Patients who received rituximab but did not achieve a complete response and are not suitable for standard-dose chemotherapy may be described as either inappropriate or ineligible to receive standard-dose chemotherapy	Round 1	7 (87.5)	Strong
• The terms "CHOP-inappropriate" and "CHOP-ineligible" describe the same patient populations	Round 1	7 (87.5)	Strong
Key demographic characteristics			
• Dose adjustment should be considered to treat:			
– Pediatric patients (0–18 years old)	Round 2	5 (62.5)	Moderate
– Geriatric patients (≥ 80 years) with poor clinical status	Round 2	8 (100.0)	Complete
Organ transplant characteristics			
• Patients who have reduced or compromised:			
– Heart allograft transplant function (LVEF < 50%)	Round 2	6 (75.0)	Moderate
– Heart allograft transplant function (LVEF < 40%)	Round 2	8 (100.0)	Complete
– Liver allograft transplant function (Child–Pugh score B [7–9] or Child–Pugh score C [10–15])[b]	Round 2	8 (100.0)	Complete
– Kidney allograft transplant function (GFR < 10 mL/min)	Round 2	5 (62.5)	Moderate
– Bone marrow transplant with leukopenia (< 2/nL)	Round 2	7 (87.5)	Strong
may be inappropriate for treatment with standard-dose chemotherapy			
EBV^+ PTLD characteristics			
• Patients with the following stages/classifications of EBV^+ PTLD (based on the 2017 WHO classification) are not appropriate candidates for standard-dose CHOP chemotherapy:	Round 1	6 (75.0)	Moderate
– Plasmacytic hyperplasia, infectious mononucleosis-like PTLD, florid follicular hyperplasia (non-destructive PTLD)			
– Classic Hodgkin lymphoma EBV^+ PTLD			

Table 2 continued

Recommendations	Source (Round 1 and/or Round 2)	Panelists who "agree" or "strongly agree" *n* (%)	Consensus rating[a]
Comorbidities/factors			
• The following aspects of a patient's medical history are important factors when considering treatment of EBV^+ PTLD with chemotherapy:			
– A history of rituximab treatment for EBV^+ PTLD	Round 1	7 (75.0)	Strong
– A history of CHOP treatment	Round 1	7 (75.0)	Strong
– Bone marrow function	Round 1	7 (75.0)	Strong
– Performance Status	Round 1	8 (100.0)	Complete
• Patients with an inadequate response to rituximab should be treated with standard-dose chemotherapy	Round 2	8 (100.0)	Complete
• Patients with an inadequate response to chemotherapy should not be treated with standard-dose chemotherapy	Round 2	5 (62.5)	Moderate
• Patients with poor bone marrow function should not be treated with standard-dose chemotherapy	Round 2	7 (87.5)	Strong
• The ECOG Performance Status can be used to help determine if standard-dose chemotherapy can be tolerated			
– In any patient	Round 1	8 (100.0)	Complete
– In a geriatric patient	Round 1	7 (87.5)	Strong
• A ECOG Performance Status response of			
– 4 (Completely disabled; cannot carry on any self-care; totally confined to bed or chair)	Round 1	7 (87.5)–8 (100.0)[c]	Strong
– 3 (Capable of only limited self-care; confined to bed or chair more than 50% of waking hours); 4 in a geriatric patient	Round 1	7 (87.5)	Strong
would indicate a patient with EBV^+ PTLD is not appropriate for standard-dose chemotherapy			
• Patients with impaired:			
– Heart function (LVEF < 40%)	Round 2	8 (100.0)	Complete
– Heart function (LVEF < 50%)	Round 2	5 (62.5)	Moderate
– Kidney function (GFR < 10 mL/min)	Round 2	7 (87.5)	Strong
– Liver function[d]	Round 2	6 (75.0)	Moderate
– Lung function[e]	Round 2	6 (75.0)	Moderate
should not be treated with standard-dose chemotherapy			

Table 2 continued

Recommendations	Source (Round 1 and/or Round 2)	Panelists who "agree" or "strongly agree" *n* (%)	Consensus rating[a]
• Patients with leukopenia[f] should not be treated with standard-dose chemotherapy	Round 2	7 (87.5)	Strong
• Patients with thrombocytopenia (< 100/nL) following bone marrow transplant may be inappropriate for treatment with standard-dose chemotherapy	Round 2	5 (62.5)	Moderate
• Patients with history of HCT and/or are within 12 months of HCT[g] may be inappropriate for treatment with standard-dose chemotherapy	Round 2	5 (62.5)	Moderate
• Patients who are frail should not be treated with standard-dose chemotherapy	Round 2	6 (75.0)	Moderate
Factors associated with chemotherapy-related mortality and morbidity			
• Risk of developing post-chemotherapy treatment infections in all patients with EBV^+ PTLD	Round 2	7 (87.5)	Strong
• Existing or previous infections	Round 2	7 (87.5)	Strong
• Prior HCT	Round 2	7 (87.5)	Strong
• Adult patients who cannot receive standard-dose chemotherapy should receive doses adapted to their GFR (e.g., 25% dose reduction of cyclophosphamide)	Round 2	5 (62.5)	Moderate
• Clinicians should collaborate with a cardiologist to determine the dose adjustment for adolescent, adult, and geriatric patients who cannot receive standard-dose chemotherapy[g]	Round 2	Adult patients: 6 (75.0) Adolescent and geriatric patients: 5 (62.5)	Moderate
• Patients with:			
– Cytopenia	Round 2	5 (62.5)	Moderate
– GFR < 10 mL/min/1.73 m^2	Round 2	6 (75.0)	Moderate
– Previous chemotherapy treatment-related toxicity (CTC grade III/IV toxicity)	Round 2	5 (62.5)	Moderate
– Comorbidities	Round 2	5 (62.5)	Moderate
should not be treated with standard-dose chemotherapy because they are at risk of treatment-related toxicity or mortality			
Adult patients who have ECOG score 0–2 should typically receive standard-dose chemotherapy	Round 2	8 (100.0)	Complete

Table 2 continued

Recommendations	Source (Round 1 and/or Round 2)	Panelists who "agree" or "strongly agree" *n* (%)	Consensus rating[a]
Patients with disease that relapsed during or whose disease was refractory to 4–8 cycles of treatment with rituximab and reduction of immunosuppression who have a good clinical status should receive standard-dose chemotherapy	Round 2	8 (100.0)	Complete

CHOP cyclophosphamide, doxorubicin, vincristine, prednisone, *COPD* chronic obstructive pulmonary disease, *CTC* common toxicity criteria, *DHC* ductus hepaticus communis, *EBV*$^+$ *PTLD* Epstein–Barr virus-positive post-transplant lymphoproliferative disease, *ECOG* Eastern Cooperative Oncology Group, *GFR* glomerular filtration rate, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *HCT* hemopoietic stem cell transplantation, *LVEF* left ventricular ejection fraction, *SpO*2 oxygen saturation, *WHO* World Health Organization

[a]A moderate consensus rating indicates that 5–6 panelists endorsed this recommendation, while a strong rating indicates that 7 panelists endorsed the recommendation. Given the small number of experts needed to achieve consensus, recommendations with moderate consensus rating should be considered thoughtfully. A complete consensus rating indicates that all panelists ($N = 8$) endorsed the recommendation. Consensus was considered not met for recommendations for which four or fewer panelists provided endorsement

[b]Statements were posed separately for Child–Pugh score B and C, but given that both achieved complete consensus, they have been combined into one recommendation

[c]Panelists could select each assessment separately and therefore consensus was calculated individually

[d]Bilirubin levels more than 3 × the upper limit, excluding liver impairment due to lymphoma infiltration or lymphoma-related DHC stenosis

[e]E.g., COPD GOLD-3, lung fibrosis, SpO2 < 85%, patients who require oxygen 100% of the time, or similar conditions

[f]Defined by baseline leukocytes < 2/nL or baseline neutrophiles < 1/nL and excluding lymphoma-related bone marrow infiltration

[g]These statements were queried separately in the round 2 survey but were combined into one recommendation given the similar topic and consensus rating. Statements were posed separately regarding adolescent, adult, and geriatric patients, but given all statements achieved moderate consensus, the recommendation is combined into one statement

consensus, with panelists agreeing that dose-adjusted chemotherapy should be considered for pediatric patients with EBV$^+$ PTLD and for geriatric populations with poor clinical status (Table 2). Panelists were also asked to identify clinical assessments that may be used to determine eligibility for standard-dose chemotherapy. Experts agreed, with strong to complete consensus, on using the following assessments in patients with EBV$^+$ PTLD: cardiological evaluation, Child–Pugh score, complete blood count, frailty assessments, glomerular filtration rate (GFR), hepatitis B/C tests using polymerase chain reaction, heart function assessment, and left ventricular ejection fraction. For geriatric patients, the panelists also recommended with moderate to complete consensus to use the Cumulative Illness Rating Scale–geriatric score, the comprehensive geriatric assessment, and performance assessments to determine eligibility for standard-dose chemotherapy.

Organ Transplant Characteristics

Five statements regarding organ transplant characteristics of patients who may be inappropriate for standard-dose chemotherapy achieved complete ($n = 2$), strong ($n = 1$), or moderate ($n = 2$) consensus (Table 2). Panelists agreed that patients with EBV$^+$ PTLD who have reduced or compromised heart function, liver function, kidney allograft transplant function, or have had a bone marrow transplant with leukopenia should not receive standard-dose chemotherapy.

EBV$^+$ PTLD Characteristics

Moderate consensus was achieved on the classifications of EBV$^+$ PTLD that may be inappropriate for chemotherapy. Panelists agreed that patients with plasmacytic hyperplasia, infectious mononucleosis-like PTLD, florid follicular hyperplasia (non-destructive PTLD), and classic Hodgkin's lymphoma EBV$^+$ PTLD should not receive standard-dose CHOP chemotherapy (Table 2).

Patient Comorbidities

Twenty-two statements describing patient comorbidities that preclude the use of standard-dose chemotherapy reached complete (n = 4), strong (n = 10), and moderate (n = 8) consensus (Table 2). Panelists agreed that patients with EBV$^+$ PTLD who are frail, have impaired organ function, or have a prior inadequate response to chemotherapy should not be treated using standard-dose chemotherapy.

Factors Associated with Chemotherapy-Related Mortality and Morbidity

In this study, 12 statements describing factors associated with chemotherapy-related mortality and morbidity achieved complete (n = 2), strong (n = 3), or moderate (n = 7) consensus (Table 2). Panelists agreed that adult patients who have an ECOG score of 0–2 should receive standard-dose chemotherapy. Additionally, panelists agreed that patients with EBV$^+$ PTLD should not receive standard-dose chemotherapy because of an increased risk of treatment-related toxicity or mortality if they also exhibit the following: thrombocytopenia (< 100 platelets/nL); GFR < 10 mL/min/1.73 m^2; or previous treatment-related toxicity (i.e., common toxicity criteria grade III/IV). Panelists also considered if a GFR < 30 mL/min/1.73 m^2 would preclude the use of standard-dose chemotherapy for EBV$^+$ PTLD but did not achieve consensus. Regarding post-treatment infection, panelists reached a strong consensus that all patients with EBV$^+$ PTLD are at risk of developing infection post chemotherapy. Patients with existing or previous infections, or those who have undergone HCT, have an increased risk of developing an infection post chemotherapy.

DISCUSSION

The modified Delphi panel is an established method that is used to achieve consensus on important topics where limited evidence exists. This study is the first to achieve expert consensus on detailed characteristics describing the EBV$^+$ PTLD patient population for whom chemotherapy may be inappropriate. The panel agreed that the terms "CHOP-inappropriate" and "CHOP-ineligible" could be used to describe patients for whom standard-dose chemotherapy is not recommended, despite these patients not achieving an adequate response to rituximab treatment. The panel also agreed that clinical characteristics such as impaired organ function, a poor ECOG performance status score, and/or a prior inadequate response to chemotherapy would preclude treatment with standard-dose chemotherapy.

The panel provided further clarity on the limited information obtained from the target literature review. Overall, articles used for survey development indicated that patients with EBV$^+$ PTLD are at a significant risk of treatment-related toxicity and mortality when undergoing chemotherapy [21, 28–32]. Chemotherapy also increases the risk of post-treatment infection and can exacerbate GvHD in EBV$^+$ PTLD following HCT [33–35]. Similarly, panelists achieved strong or moderate consensus on four statements regarding post-chemotherapy mortality and morbidity, agreeing that all patients with EBV$^+$ PTLD, especially HCT recipients, are at risk of developing infections post chemotherapy treatment. The literature suggests that patients with an aggressive form of EBV$^+$ PTLD or with a rapidly declining clinical status, including pediatric populations, may benefit upfront from chemotherapy [11, 35]. However, guidance was not provided on dose. The panel provided additional clarification and recommended that pediatric and geriatric patients with poor clinical status should receive dose-adjusted chemotherapy.

A number of statements in the round 2 survey, including demographic characteristics of patients who should receive dose-adjusted chemotherapy, socio-demographic factors

determining CHOP eligibility, and the type of transplants that may make CHOP inappropriate for treatment, did not achieve panel consensus (Supplementary Material Table S3). These statements were based on open-ended responses that were submitted during round 1, and in general, panelists were not able to provide significant input on these based on varied clinical experience.

Certain clinical and demographic characteristics identified in this study (i.e., impaired organ or bone marrow function, a high ECOG score, or a history of HCT) would categorize a considerable number of patients as being inappropriate for standard-dose chemotherapy. Further, patients with EBV$^+$ PTLD who do respond to chemotherapy may need multiple rounds of treatment [36], which may increase the risk of treatment-related adverse events and may lead to reduced quality of life with long-term adverse consequences [37]. Therefore, it is critical to provide these patients with well-tolerated, alternative treatments with reduced risk of treatment-related toxicity. There are a limited number of chemotherapy-sparing treatment options being studied for EBV$^+$ PTLD following HCT or SOT, including the adoptive transfer of EBV-specific cytotoxic T lymphocytes (CTLs)—an approach that is already incorporated into the BSH, ECIL, and NCCN guidelines as a rescue therapy for this disease [10–12]. Cellular therapy using autologous and HCT donor-derived EBV-CTLs has resulted in complete and partial responses with minimal treatment-related toxicity [4, 38]. Although there are no therapies currently approved for EBV$^+$ PTLD, the ongoing phase III ALLELE trial (NCT03394365) continues to evaluate the efficacy and safety of allogeneic EBV-CTL therapy in allogeneic HCT or SOT recipients with EBV$^+$ PTLD following failure of rituximab or rituximab plus chemotherapy treatments.

This modified Delphi panel study has several potential limitations. The panel consisted of eight clinical experts, which is a slightly smaller number than the recommended 10–15 [39, 40]. EBV$^+$ PTLD is an ultra-rare disease, with an incidence of less than 1 in 1 million. Given this ultra-rarity, these clinical experts are among the top treaters of the disease in Europe. Consensus recommendations have been outlined in this study by clinical experts for Europe; however, given that the treatment paradigm is similar in other regions and there are no treatment options in patients with relapsed/refractory EBV$^+$ PTLD, the recommendations are applicable more globally.

CONCLUSION

This modified Delphi study achieved expert consensus on recommendations that characterize patients with EBV$^+$ PTLD for whom chemotherapy may be inappropriate. These statements will provide guidance for assessing chemotherapy eligibility in a real-world clinical setting. This paper identifies important factors that should be accounted for when choosing a treatment regimen for patients with EBV+ PTLD.

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