



The Short-Term Efficacy and Safety of Brentuximab Vedotin Plus Cyclophosphamide, Epirubicin and Prednisone in Untreated PTCL: A Real-World, Retrospective Study

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ABSTRACT

Introduction: Brentuximab vedotin (BV) showed high overall remission rates in refractory/relapsed classical Hodgkin's lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL). Although the efficacy of BV has been reported in clinical trials, its efficacy as a frontline therapy in real world for patients with CD30 positive subtypes of non-Hodgkin's lymphoma (NHL) such as peripheral T-cell lymphoma with T-follicular helper cell (TFH) phenotype (PTCL, TFH), anaplastic large-cell lymphoma (ALCL) and angioimmunoblastic T-cell lymphoma (AITL) in China has not been well documented.

Methods: Analysis of a real-world, observational, retrospective case series in patients

Xiaomeng Feng and Wei Guo are co-first authors of this article.

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suffering from AITL, sALCL and peripheral T-cell lymphoma with T-follicular helper phenotype (PTCL-TFH) and other types of PTCL treated with BV in frontline treatment was conducted. The patients were given treatment from May 2020 till June 28, 2021. All patients were pathologically diagnosed to have PTCL before treatment and expressed CD30. Patients received BV (1.8 mg/kg) combined with CEP (cyclophosphamide, epirubicin, prednisone acetate every 3 weeks). The primary endpoint was objective response rates (ORR), and secondary endpoints were duration of response and incidence of adverse events (AEs). Exploratory endpoints such as progression-free survival (PFS) are discussed even though after such a short period.

Results: Nineteen patients completed ≥ 1 cycles of BV-CEP treatment (16 cases completed ≥ 4 cycles, 3 cases only completed 1 cycle). Among them, the ORR reached 89.5% [CR 52.7%; partial response (PR) 36.8%]. In the ALCL group, CR reached 100% with the median duration of response of up to 8 months, while in the AITL group, the ORR was 75% and 2 patients had disease progression after treatment with BV + CEP. We also observed that BV-CEP may extend the PFS compared to traditional chemotherapy such as the CHOEP regimen (BV-CEP: not evaluable, CHOEP: 6.5 months), although the median follow-up was only 6.7 months. Adverse events (AEs), including incidence and severity of febrile neutropenia

(26% patients in the BV-CEP group and 30% in the CHOEP group), were similar between groups. There was no incidence of AEs leading to treatment withdrawal or death under BV-CEP treatment.

Conclusion: BV is a promising treatment in patients with ALCL, AITL and PTCL-TFH in frontline treatment settings.

Keywords: Brentuximab vedotin (BV); Cyclophosphamide; Epirubicin; Peripheral T cell lymphoma; Prednisone acetate (CEP)

Key Summary Points

Why carry out this study?

Chemotherapy alone is not effective in peripheral T-cell lymphoma (PTCL).

Brentuximab vedotin (BV) combined with chemotherapy has been confirmed in clinical trials and has a significant effect on CD30 + PTCL.

What was learned from the study?

Our research verifies that BV has a significant effect on the treatment of CD30 + PTCL in the real world, especially the type of anaplastic large cell lymphoma (ALCL).

BV combined with chemotherapy is mostly tolerable in PTCL.

The relationship between the efficacy of BV combined chemotherapy and the level of expression of CD30 is worth exploring.

contrarily, it is high in the Asian populations, contributing to 15–20% of all NHLs [2]. The median age is 50–60 years old, and the incidence is higher in men [3]. Common aggressive subtypes include peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), extranodal NK/T-cell lymphoma (ENKTL) nasal type, adult T-cell lymphoma (ATL), anaplastic lymphoma kinase (ALK) positive anaplastic large cell lymphoma (ALCL) and ALK–ALCL.

At present, anthracycline- or gemcitabine-based chemotherapy is adopted for frontline treatment of PTCL. ALK + ALCL has a better prognosis than other PTCLs when treated with CHOEP [4, 5], while other types only with an overall response rate (ORR) of 70–80%, and almost 70% patients have recurrence and progression [6, 7]. The efficacy of traditional chemotherapy as salvage therapy in this group of patients is poor, and the median overall survival (OS) is only about 6 months [8]. Consolidation with allogeneic hematopoietic stem cell transplantation (HSCT) has been reported to slightly improve progression-free survival (PFS) (3-year OS 73%; 3-year PFS 53%) [9–11], and in relapse/refractory (R/R) patients, it has a low benefit with 3-year event-free survival (EFS) of 43% and a 3-year OS of 57%, while the risk of treatment-related death is high. In other previous studies, the addition of alemtuzumab, pralatrexate and romidepsin failed to improve patient survival; however, it increased the incidence of adverse events [12–14].

In recent years, due to the application of newer approaches to targeted therapy, drugs including PD-1/PD-L1 inhibitors (geptanolimab), PI3K inhibitors (copanlisib) and other novel drugs such as Selinexor are being used for the treatment of PTCL either alone or in combination with other chemotherapeutic drugs [15–17]. Among the novel targets, CD30 overexpressing cells provide an anti-apoptotic survival advantage and could be targeted in various subtypes of lymphoma, including classic Hodgkin's lymphoma (cHL), ALCL and primary cutaneous CD30-positive T-cell lymphoproliferative diseases [18]. In other subtypes of lymphomas, the expression of CD30 may reach up

INTRODUCTION

Peripheral T-cell lymphoma (PTCL) generally refers to mature T/natural killer (NK)-cell lymphoma that originates from post-thymic to a heterogeneous malignant lymphoproliferative disease [1]. The incidence of PTCL is low in the Western world, accounting for about 2–10% of all non-Hodgkin's lymphomas (NHL), but

to 64% in PTCL-NOS, 43% in AITL and 80% in ENKTL [19].

Brentuximab vedotin (BV) is a conjugate of anti-CD30 monoclonal antibody and anti-tubulin monomethyl auristatin E (MMAE) that could bind to CD30 on the surface of tumor cells leading to destabilization of the microtubules, arrest of cell cycle and cell apoptosis [20]. Previous clinical trials had established the clinical efficacy of BV in combination with chemotherapy in patients with relapsed refractory (R/R) systemic ALCL, PTCL, PTCL-NOS, AITL, ENKTL and adult T-cell leukemia/lymphoma (ATLL) [21, 22]. In China, BV is approved by the national medicinal products administration (NMPA) for the treatment of CD30-positive lymphomas based on evidence from clinical trials [23]. However, the effectiveness of BV in real-world treatment settings for PTCL in China is yet to be ascertained. Hence, we performed a retrospective study from clinical databases to evaluate the short-term effectiveness of BV in PTCL patients to confirm its effectiveness in real-world settings.

METHODS

Study Design and Population

An observational retrospective study was performed to assess the safety and effectiveness of BV in previously untreated patients with PTCL who received ≥ 1 cycles of BV-CEP treatment from May 2020 onwards. Data from patients with a pathological diagnosis of PTCL with positive expression of CD30 were extracted from the hospital registry database. We also included patients with PTCL who were treated with CHOEP at the same time as a control group to compare the safety and efficacy of the two programs. The study was approved by the ethics committee of the First Hospital of Jilin University 2021-468, and the need for informed consent was waived by the ethics committee since only anonymized patient data were used for the study. The study was performed in accordance with the Declaration of Helsinki.

All the patients were subjected to bone marrow biopsy to ascertain the involvement of

bone marrow, and positron emission tomography-computed tomography (PET-CT) evaluation was performed at the time of diagnosis. PET CT was also performed after the course of treatment to evaluate the effectiveness of treatment. The patients included in the study were treated with BV (1.8 mg/kg) in combination with CEP (cyclophosphamide 750 mg/m², epirubicin 75 mg/m², prednisone 60 mg/m², every 3 weeks) based on the clinical judgment of the treating physician. Treatment with chemotherapy was temporarily terminated in patients with agranulocytosis with severe infection [grade 4 related adverse events (AEs)], and the treatment was resumed only after the clinical improvement in agranulocytosis and infection. The clinical data extracted from the database include basic demographic details and clinical data including previous treatment.

Study Outcomes

The primary endpoint assessed in this study was the ORR achieved during the treatment with BV, and secondary endpoints were duration of response and incidence of adverse events (AEs). Exploratory endpoints such as progression-free survival (PFS) are discussed even though after such a short period.

Statistical Analysis

Basic statistical analysis was performed, and the categorical variables were expressed as frequencies and continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR) depending on the distribution. ORRs were calculated based on the number of patients with complete response (CR) and partial response (PR) and were provided as percentage. We did formal statistical tests for PFS for the secondary endpoints. For the primary efficacy analysis, we used the stratified log-rank test to compare the difference in PFS between the two treatment groups. All the statistical analyses were performed with SPSS statistics 22 software and Graphpad prism 6.0 software.

RESULTS

Study Patients

Nineteen patients, who had completed ≥ 1 cycles of BV-CEP treatment, including both males and females [7 ALCL (6 ALK-positive and 1 ALK-negative), 8 AITL and 1 PTCL-TFH, 2 NK/T, 1 *Mycosis fungoides* (MF)], featured by untreated, advanced clinical stage and high international prognostic index (IPI) score, were included for the study. (Please refer to the table in the Supplementary Material for more details.) Eighteen patients (94.7%) were identified with Ann Arbor stage III/IV, 14 (73.7%) patients had B symptoms (fever, drenching night sweats and loss of $> 10\%$ of body weight over 6 months), and 15 (78.9%) patients had extranodal infiltration. Further 13 patients (68.4%) had an International Prognostic Index (IPI) score ≥ 3 , and 14 patients (71.4%) had higher lactate dehydrogenase (LDH) values (Table 1). All the patients had higher than normal $\beta 2$ -MG values (100%), which suggests that the patients may not derive benefits from monotherapy with chemotherapeutic agents.

Response to Treatment

Nineteen patients completed ≥ 1 cycles of BV-CEP treatment (16 cases completed ≥ 4 cycles, 3 cases only completed 1 cycle). At a median follow-up of 6.7 months (range 1.3–9.7) for the entire cohort, all patients were evaluated for response. Among them, the ORR reached 89.5% (CR 52.7%; PR 36.8%) (Table 2). In the ALCL group, CR reached 100%, with a median duration of response of up to 8 months (Table S1 Supplementary Material). In the AITL group, the ORR was 75% (CR 25%; PR 50%) (Figs. 1, 2) and the median duration of response up to 6 months, while 2 patients experienced progression after BV + CEP. The remaining 25% of the patients had disease progression. One subject developed a new target lesion, and another subject developed an increase in the size of the primary lesion. In the PTCL-TFH group, one elderly female patient with poor functional status at baseline (ECOG > 2 points) who

received BV + CEP treatment had CR after four courses of treatment and then received chidamide for maintenance with a subsequent duration of response of up to 6 months. Two other high-risk ENKTLs and one case of MF patients' lesions reduced by $> 50\%$ after only one cycle of BV-CEP, but still needed long-term observation of later efficacy and safety.

Compared to the CHOEP treatment during the same period ($n = 14$, Table 3), BV-CEP may improve response rates and delay disease progression (ORR 50%, PD 50% in CHOEP, Fig. 3). During the follow-up period, no deaths occurred in the BV-CEP group, while four patients (28.5%) died in the CHOEP group. The median PFS was not reached in the BV-CEP group, while 6.5 months in the CHOEP group, which may indicate that BV-CEP may extend the PFS of PTCL patients [HR 0.21 (95%CI 0.06–0.71); $p = 0.026$] (Fig. 4).

We also explored the relationship between CD30 expression and efficacy (Table 4). The results showed that, among these patients, the CD30 expression level of ALCL is relatively high, and 80% of them have expression levels $> 80\%$. The use of BV has achieved very significant curative effects. However, in AITL, we found that the overall expression level is low, ranging from 2% to 40%, and there is no obvious correlation with the therapeutic effect.

Safety

For the safety assessment patients who have received at least one cycle of BV treatment were included (Table 5). In general, the AEs of BV combined with chemotherapy were mostly tolerable. The most common adverse effects occurring in patients were peripheral neuropathy, but no patients had neuropathy of grade 3 or above; the second most common adverse reaction was gastrointestinal reactions, including vomiting and diarrhea, especially in the AITL group. In addition, grade > 3 neutropenia occurred in almost 26.3% of the patients (Table 5), which is similar to the CHOEP group in our center (30%). One patient with ALCL had a severe respiratory infection and the pathologic testing showed *Pneumocystis pneumonia*

Table 1 Baseline of the 19 patients treated by BV-CEP

Characteristics		N (%)
Age	Median age	53 (16–77 years)
	> 60 years	5 (26.3%)
	≤ 60 years	14 (73.7%)
Sex	Male	10 (52.6%)
	Female	9 (47.4%)
Type	ALCL	7 (36.8%)
	AITL	8 (42.1%)
	PTCL	1 (5.3%)
	NK/T	2 (10.5%)
	MF	1 (5.3%)
Stage	II	1 (5.3%)
	III/IV	18 (94.7%)
ECOG	< 2	12 (63.2%)
	≥ 2	7 (36.8%)
B symptoms	No	5 (26.3%)
	Yes	14 (73.7%)
Extranodal sites	No	4 (21.1%)
	Yes	15 (78.9%)
Bone marrow involvement	No	17 (89.5%)
	Yes	2 (10.5%)
LDH	ULN	5 (28.6%)
	> ULN	14 (71.4%)
β2-MG	ULN	0
	> ULN	19 (100%)
IPI	0–1	1 (5.3%)
	2	5 (26.3%)
	3–5	13 (68.4%)

(PCP). After anti-infective treatment, the respiratory function was restored and treatment was continued. All patients recovered after

management and treatment according to the guidelines. There were no incidences of AEs leading to treatment withdrawal or death.

Table 2 Efficacy at end of treatment

Efficacy	Total (%)	ALCL	AITL (%)	PTCL*
ORR	89.5	100.0%	75.0	100.0%
CR	52.7	100.0%	25.0	25.0%
PR	36.8	0	50.0	75.0%
PD	10.5	0	25.0	0

PTCL* including three types: PTCL-TFH, ENKTL, MF

DISCUSSION

Most of the patients receiving BV treatment in our center are clinically high-risk patients with advanced clinical stage, severe symptoms and high IPI score, who have difficulty benefiting from chemotherapy alone. Relapse and

refractory patients are refractory to frontline treatment or relapse after multi-line treatment. However, these patients had a high overall response rate of > 89% to BV and good tolerance. No adverse reactions related to drug withdrawal or death occurred.

In our cohort, the ORR and CR in the ALCL group achieved 100% within the median follow-up of 8.5 months (range 4.9–9.5). This is remarkably higher than for the traditional chemotherapy regimen with fewer adverse events, which may produce general efficacy only for sALCL with low IPI score (< 2) and ALK-positive status with ORR 70–80% [6, 24, 25]. Our study is in line with the results of the phase 3 ECHELON-2 clinical trial. The ECHELON-2 study shows that BV-CEP regimens have an impressive efficacy with ORR of 83% and CR of 68% in newly diagnosed patients mainly including > 70% ALCL population with

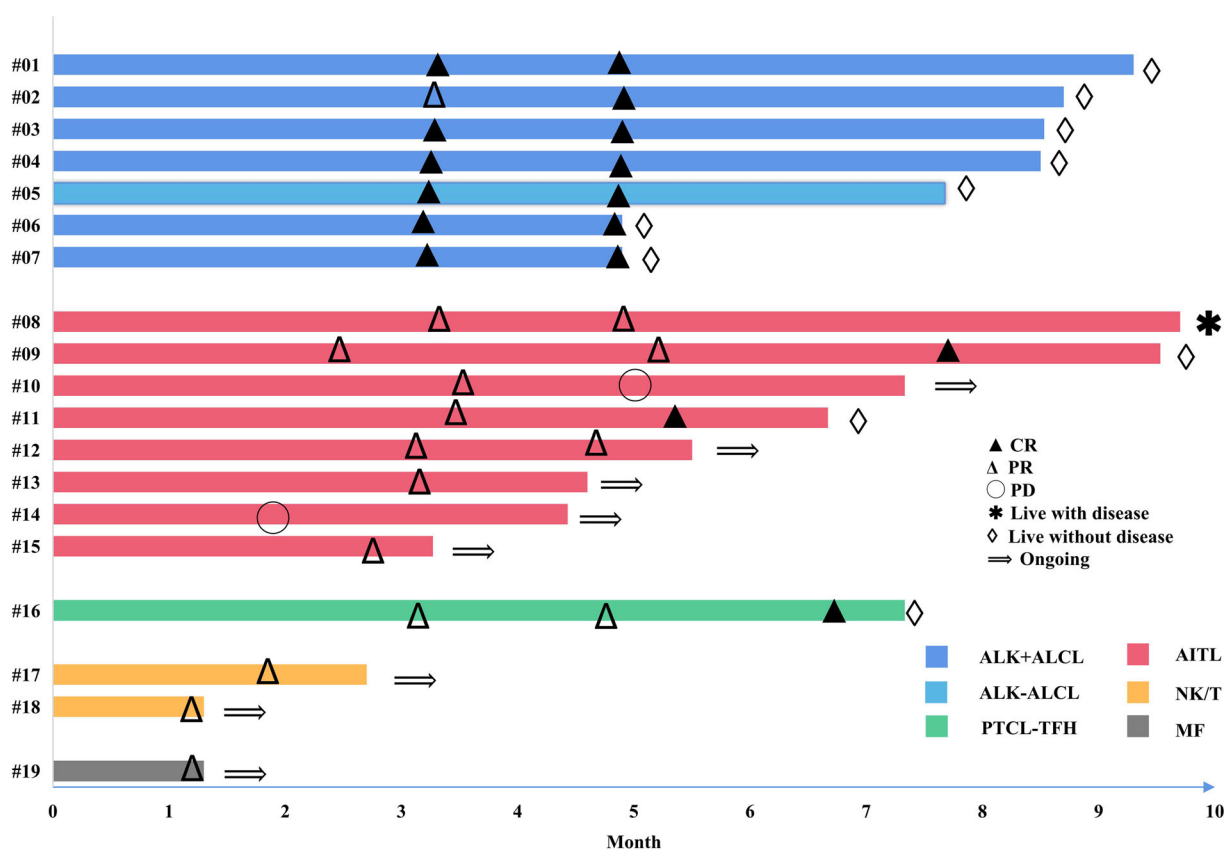


Fig. 1 Treatment and survival status

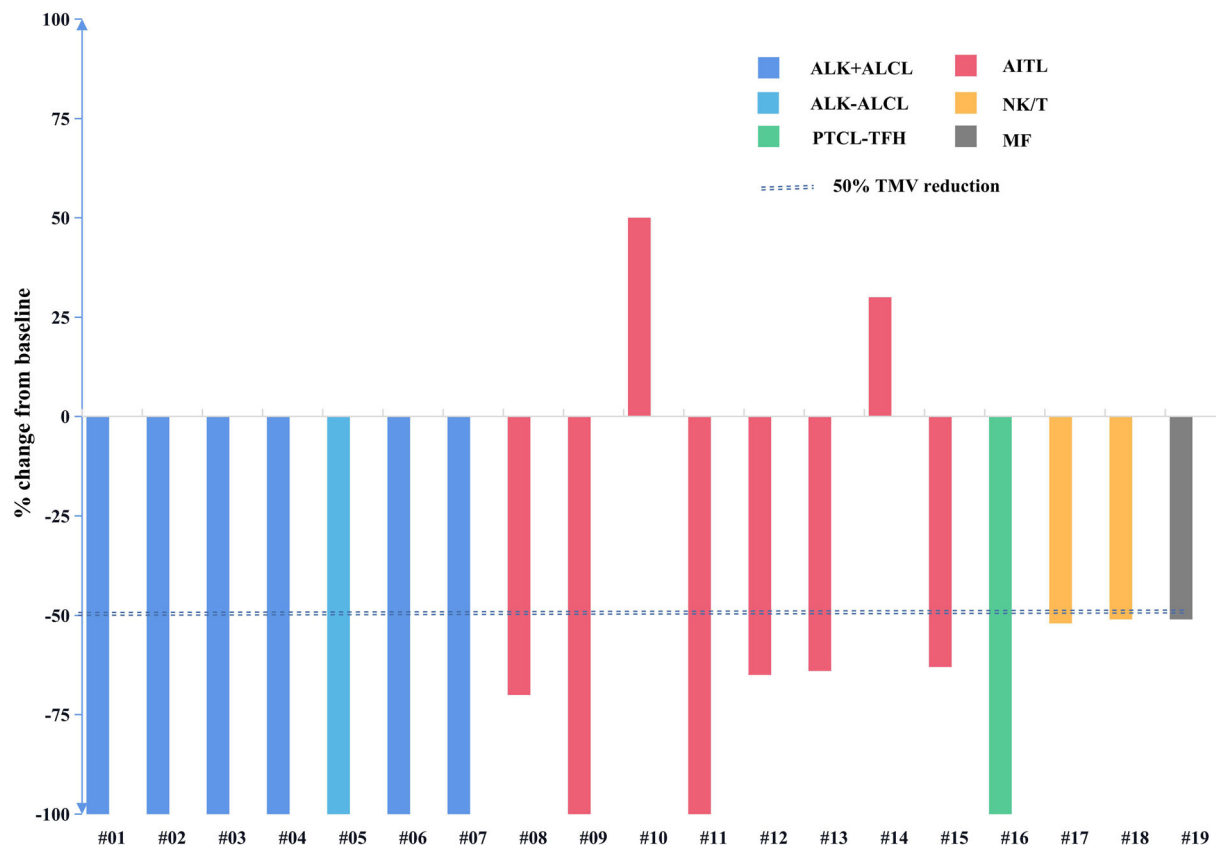


Fig. 2 Objective response rates to BV-BEP combination therapy. Displayed is the change in target lesion diameter from baseline (%) by PET-CT or CT; negative values

indicate tumor shrinkage. Seventeen of 17 (89.5%) PTCL patients responded to BV-based combination therapy and achieved > 50% tumor volume reduction

a median PFS of 63.5 months after 5 years of follow-up [26]. However, in our study, after completing six cycles of BV combination therapy, patients underwent oral chidamide treatment for maintenance. Patients with extended follow-up may demonstrate better PFS and OS. Hence, no further stem cell transplantations were carried out.

In the AITL group, ORR and CR are relatively lower. The findings indicate that there is obvious heterogeneity, and it may be difficult to achieve deep remission after treatment with BV in AITL. However, considering these patients are often elderly and high risk, combined with having multiple complications, only one young female patient completed the consolidation treatment of auto-ASCT after complete response to BV-CEP. Now she is living without diseases, suggesting that BV can be used as a bridge

regimen for transplantation. Findings indicate that BV used as a bridge therapy before HSCT has increased the chances of survival for lymphoma patients. This salvage therapy along with HSCT has been performed as a second-line treatment regimen. In a nutshell, exploring more effective combinations of targeted therapy and chemotherapy, such as epigenetic inhibitors or immune checkpoint inhibitors, would be beneficial.

Further analysis of the intensity of CD30 expression was conducted. The expression level of CD30 is generally high in ALCL (almost 90%–100%) and low in AITL (mostly between 10–40%), which may imply that BV may produce better efficacy in CD30 high-expressed tumor type, like ALCL [27]. However, in the AITL group, our study also found that even patients with low expression levels (< 10%) still

Table 3 Baseline of the 14 patients treated by CHOEP

Characteristics		BV-CEP (<i>n</i> = 16)	CHOEP (<i>n</i> = 14)
Age	Median age	49.5 (16–77 years)	55 (38–70 years)
	> 60 years	3 (18.8%)	5 (35.7%)
	≤ 60 years	13 (81.2%)	9 (64.3%)
Sex	Male	8 (50.0%)	7 (50.0%)
	Female	8 (50.0%)	7 (50.0%)
Type	ALCL	7 (43.7%)	6 (42.3%)
	AITL	8 (50.0%)	7 (50.6%)
	PTCL	1 (6.3%)	1 (7.1%)
Stage	II	1 (6.3%)	1 (7.1%)
	III/IV	15 (93.7%)	13 (92.9%)
ECOG	< 2	11 (68.7%)	4 (28.6%)
	≥ 2	5 (31.3%)	10 (71.4%)
IPI	0–1	1 (6.3%)	1 (7.1%)
	2	4 (25.0%)	3 (21.5%)
	3–5	11 (68.7%)	10 (71.4%)

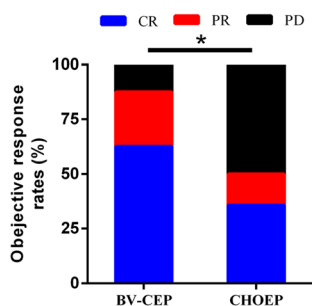


Fig. 3 ORR comparison between BV-CEP vs. CHOEP

have a significant response to BV, which is consistent with the previous finding of an exploratory correlation between CD30 expression and efficacy [28]. This may imply that clinical decision of using BV on the basis of CD-30 expression may not be feasible.

We also explored other types of PTCL, such as PTCL-TFH, NK/T and MF. One case of clinically high-risk elderly PTCL-TFH achieved CR after six courses of BV combination therapy, while two patients with NK/T and one patient with MF are under treatment.

Our study explored the use of BV in the real world. Although the sample size was small, it involved different PTCL subtypes. Compared with the CHOEP regimen treatment data in our center, preliminary results show that BV-CEP may extend the PFS. Compared with the results of a multicenter real-world study of CHOPE in the treatment of newly treated patients with PTCL in the US [29], our study indicated a remarkable efficacy of BV-CEP in PTCL despite our patients having higher IPI scores and advanced stage. In our study, treatment with BV in patients with PTCL caused mild and tolerable side effects. Under proper management, most

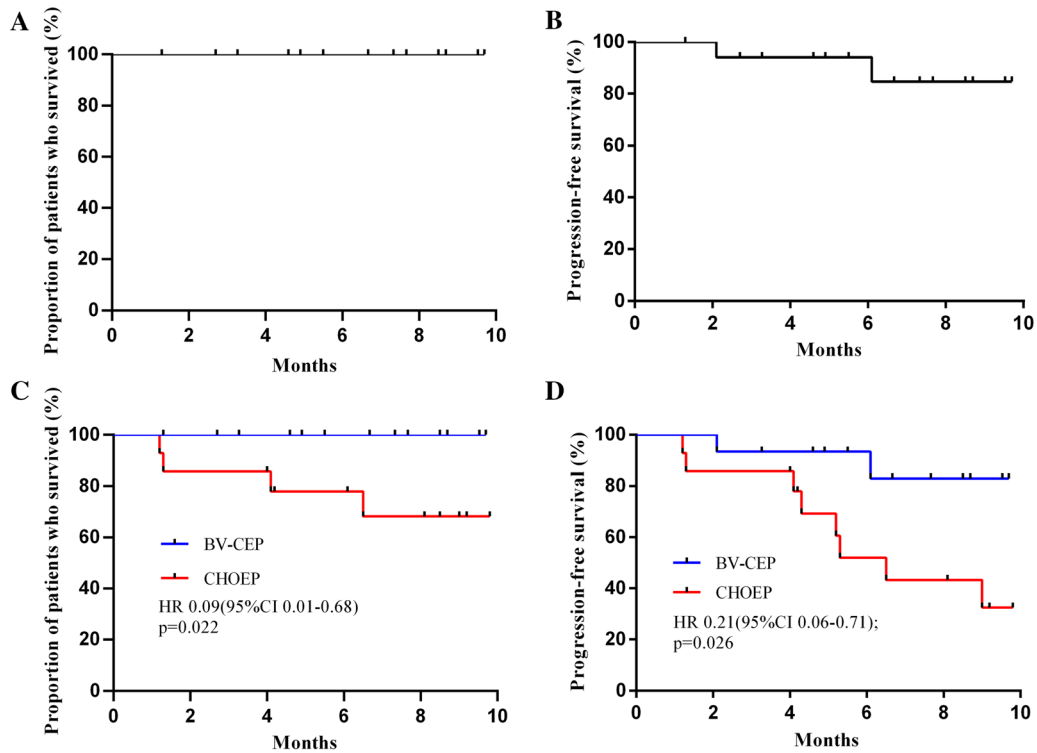


Fig. 4 **A** The OS curve in BV-CEP group. **B** HR for treatment with BV-CEP vs. CHOEP and the 95% CIs were computed from a log-rank test in terms of OS. **C** PFS

curve in BV-CEP group. **D** HR for treatment with BV-CEP vs. CHOEP and the 95% CIs were computed from a log-rank test in terms of PFS. *HR* hazard ratio

Table 4 ORR and CD30 expression score

CD30 expression score	ORR, <i>n</i> (%)			
	Total	ALCL	AITL	PTCL*
0–1	10 (52.6%)	1 (12.5%)	6 (85.7%)	3 (75.0%)
2–3	2 (10.6%)	0	1 (14.3%)	1 (25.0%)
4	7 (36.8%)	7 (87.5%)	0	0

CD30 score 0: expression \leq 19%, CD30 score 1: expression in 20–39%, CD30 score 2: expression in 40–59%, CD30 score 3: expression in 60–79%, CD30 score 4: expression in \geq 80%. PTCL* including three types: PTCL-TFH, ENKTL, MF

patients can complete chemotherapy on time. The limitations of our research are mainly in the small sample size and short follow-up time. In the future, we need to further expand the sample size and extend the follow-up time to verify the long-term efficacy of BV in real-world clinical practice, especially for various subtypes of PTCL.

CONCLUSION

To conclude, treatment with BV in combination with chemotherapy is effective in different subtypes of PTCL with relatively long duration of response, which could be sustained by maintenance therapy. Further long-term follow-

Table 5 AEs

AEs	Grade 1/2	Grade 3	Grade 4
Neutropenia	8 (42.1%)	6 (31.6%)	5 (26.3%)
Thrombocytopenia	11 (57.9%)	5 (26.3%)	3 (15.8%)
Anemia	13 (68.4%)	6 (31.6%)	0
Diarrhoea	18 (94.7%)	1 (5.3%)	0
Infection	14 (73.7%)	5 (26.3%)	0
Vomiting	18 (94.7%)	1 (5.3%)	0
PN	19 (100.0%)	0	0

up studies with larger sample sizes are required to substantiate our results.

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Author Contributions. All named authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Xiaomeng Feng, Wei Guo and Jia Li. The first draft of the manuscript was written by Xiaomeng Feng, and all authors commented on previous versions of

the manuscript. All authors read and approved the final manuscript.

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Compliance with Ethics Guidelines. The study was approved by the ethics committee of the First Hospital of Jilin University 2021-468, and the need for informed consent was waived by the ethics committee since only anonymized patient data were used for the study. The study was performed in accordance with the Declaration of Helsinki.

Data Availability. All data generated or analyzed during this study are included in this published article/as supplementary information files. See Table S1 in the Electronic Supplementary Material for details.

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