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Brentuximab Vedotin Monotheraphy in Relapsed/Refractory T Cell Lymphoma Setting-Real Life Data

Relaps /Refrakter T Hücreli Lenfomada Brentuksimab Vedotin Monoterapisi-Gerçek Yaşam Verisi

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Brentuximab Vedotin Monotheraphy in Relapsed/Refractory T Cell Lymphoma Setting-Real Life Data

ABSTRACT

Objective: We present data of patients with relapsed/ refractory T cell lymphomas treated with brentuximab vedotin (BV) in real-world practice.

Material and Method: This study is an observational, multi-center, retrospective study. The data of patients (n=17) treated with BV alone from January 2014 until July 2020 in thirteen centers from Turkey were collected.

Results: Bv was given as salvage chemotherapy to 17 patients with median age of 53. Nine (52.9%) patients had diagnosis of peripheral T cell lymphoma, not otherwise specified; 8 (47.1%) patients had anaplastic large T cell lymphoma. The median follow-up of the cohort was 20 months. Nine (52.9%) patients had complete response, 5 (29.5%) had partial response, 3 (17.6%) had progressive disease. The safety results aligned with the established profile of BV, included 2 pneumonia and 1 thrombocytopenia with grade 4. The median progression free survival of the cohort was 10 months. BV cycle and response to BV therapy were found to have an effect on the univariate analysis.

Conclusion: In patients with relapsed/ refractory T cell lymphomas, BV seems to have convincing antitumor activity with favorable safety profile.

Keywords: Brentuximab vedotin, relapse, T cell lymphoma.

ÖZET

Amaç: Brentuksimab vedotin (BV) ile tedavi edilen Relaps /Refrakter (R/R) THL'li hastaların gerçek yaşam verilerini sunmayı amaçladık.

Gereç ve Yöntem: Bu çalışma gözlemsel, çok merkezli, retrospektif bir çalışmadır. Ocak 2014'ten Temmuz 2020'ye kadar Türkiye'deki on üç merkezde yalnızca BV ile tedavi edilen tüm hastaların (n=17) verileri toplandı.

Bulgular: Ortanca yaşı 53 olan 17 hastaya kurtarma kemoterapisi olarak BV verildi. Dokuz (%52,9) hastaya periferik T hücreli lenfoma, diğer türlü sınıflandırılamayan tanısı konurken, 8 (%47,1) hastaya anaplastik büyük T hücreli lenfoma tanısı konuldu. Kohortun ortanca takip süresi 20 aydı. Dokuz (%52,9) hastada tam yanıt, 5 (%29,5) hastada kısmi yanıt, 3 (%17,6) hastada ilerleyici hastalık görüldü. Güvenlik verileri BV bilinen profiliyle tutarlıydı, 2 pnömoni ve 4. dereceli 1 trombositopeniyi içeriyordu. Grubun medyan progresyonsuz sağkalımı 10 aydı. Siklus sayısının BV tedavisine yanıtın üzerinde etkili olduğu değişkenli analiz ile bulundu.

Sonuç: R/R THL'leri olan hastalarda BV olumlu güvenlik profili ile tatmin edici antitümör aktivitesine sahip olduğu görülmektedir.

Anahtar Sözcükler: Brentuksimab vedotin, nüks, T hücreli lenfoma.

Introduction

T-cell lymphomas (TCLs) are a diverse category of non-Hodgkin lymphomas, encompassing many subclasses such as angioimmunoblastic T-cell lymphoma (AITL), anaplastic large-cell lymphoma (ALCL), mycosis fungoides (MF) and others (1). TCLs respond poorly to traditional chemotherapeutics, and their prognosis is dismal. Currently, first-line regimens with low response rates include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) based regimens (2). Since most patients who receive first-line medications experience refractoriness or early recurrence, multiple trials have tested innovative medicines for these patients in recent years (3).

Anti-CD30 monoclonal antibody and cytotoxic antitubulin agent monomethyl auristatin E (MMAE) combine to form the antibody-drug combination product known as BV (4). After at least one previous multidrug chemotherapy regimen failed, the FDA authorized BV in August 2011 for the treatment of individuals with systemic ALCL. About malignant lymphoid tumors, BV has some advantages: a) has a stronger and longer duration of activity, b) has relatively stable concentrations, c) is less toxic to normal cells, d) may eradicate CD30+ non-malignant cells in the microenvironment that have protumor effects (5). In one study, 34 patients with at least two lines of treatment history and resistant CD30+ PTCL were treated with single-agent BV; 24% achieved complete remission (CR), and 14% achieved partial remission (PR). Among 13 patients diagnosed with AITL, five had a CR, and two had a PR. Of the twenty-one patients with PTCL, NOS, three achieved a CR and four a PR. In this trial, median progression-free survival (PFS) was 6.7 and 1.6 months, respectively (6). It is known that prospective randomized study results and real-life experiences could be different.

Here, we conducted a retrospective multicenter study on a cohort of relapsed or refractory TCLs patients treated with BV monotherapy. This study aimed to report real-life outcomes of BV monotherapy.

Material and Method

This is a retrospective, multi-center, observational research. We collected the data of patients (n: 17) treated with BV alone in thirteen centers from Türkiye between January 2014 to July 2020 using an automated database and a methodical chart review. Immunohistochemistry study was determined by each center. Refractory illness was defined as a recurrence that occurred within six months of the last therapy and less than a partial response (PR). Relapsed disease was defined as a relapse following at least a partial response.

Any drug-related side effects during the BV therapy were recorded. The clinical importance of adverse events was assessed. (For example, grade 3-4 hematologic toxicity or other severe effects that necessitated the termination or discontinuation of BV medication)

The response rate was assessed at the discretion of the individual physician using the 2007 updated response criteria for malignant lymphoma (7) and the International Working Group revised response criteria for malignant lymphoma (8).

The complete response rate (CRR) was defined as the proportion of CR found during BV therapy. The ORR was computed by summing the CR and PR rates obtained during BV treatment. Progression-free survival (PFS) is calculated from the start of BV therapy to progression, relapse, or death from any cause. Survival was calculated based on the final follow-up visits throughout the research period or if medication was changed for reasons other than progression or regression. Overall survival (OS) was estimated using survivors' most recent follow-up visit from the start of BV treatment to death from any cause.

The study was carried out in accordance with the Declaration of Helsinki and with the approval of the ethics committee of Abdurrahman Yurtaslan Oncology Research and Training Hospital (ethical approval no: 2023-02/03)

For analysis, IBM SPSS, Version 26.0 (IBM Corp., Armonk, N.Y., USA) was used. To demonstrate patient and illness characteristics, descriptive statistics were used. The median (minimum-maximum) value for continuous variables was used. Categorical variables were presented as numbers and percentages. PFS was estimated using Kaplan-Meier survival analysis. To assess the parameters impacting PFS, Cox regression analysis was used. Initially, univariate analysis was performed, and components with p-values less than

0.25 were included in multivariate analysis. $p < 0.05$ was considered statistically significant.

Results

Nine (52.9%) patients had a diagnosis of PCTL, NOS whereas, 8 (47.1%) patients had anaplastic large T cell lymphoma. The median age was 53 (21-78) and there was a male predominance (n=11(64.7%)). All patients were positive for CD30 by immunohistochemistry. The median follow-up of the cohort was 20 (4-87) months. Table I summarizes the patients' baseline demographic data and clinical characteristics.

Table I. Demographic Data and Patients' Clinical Features

Parameters	N=17 100%)
Gender (Male/Female)	11/6
Age (median)	53 (21-78)
Follow-up duration (months)	20 (4-87)
B symptom	8 (47.1%)
Bulky disease	3 (17.6%)
Performance (ECOG ≥2)	5 (29.4%)
Subtype	
Peripheral T cell NOS	9 (52.9%)
Anaplastic large T cell	8 (47.1%)
Advanced Stage (Ann Arbor 3-4)	13 (76.5%)
Extranodal involvement	8 (47.1%)
Bone marrow involvement	6 (35.3%)
Risk Scores	
International Prognostic Index (High-intermediate, High)	6 (35.3%)
AA- International Prognostic Index (High-intermediate, High)	7 (41.1%)
Prognostic Index for PTCL-U(PIT) (Group 3-4)	9 (52.9%)
International T cell lymphoma Project (Group 3-4)	9 (52.9%)

AA: age-adjusted, ECOG: Eastern Cooperative Oncology Group, NOS: not otherwise specified.

BV was given at a dose of 1,8 mg/kg every three weeks until progression or unacceptable toxicity for salvage chemotherapy to 17 patients.

After the evaluation of BV response 9 (52.9%) patients had a complete response, 5 (29.5%) had a partial response, and 3 (17.6%) had progressive disease. Patients had median 2 (1-6) line treatments, 16 (94.1%) received conventional chemotherapies and 1 (5.9%) received autologous stem cell transplant before BV initiation. The median age of BV initiation was 56 (21-78). BV was administered for median 6 (1-19) cycles. BV was utilized as salvage treatment before ASCT (bridge to SCT setting) in 7 (17.6%) patients and before allo-SCT in 1 (5.9%) patient. BV was discontinued in patients mostly for ASCT and progression. The BV data is demonstrated in Table II.

Table II. Brentuximab Therapy data

	N=17 (100%)
Age (median)	56 (21-78)
Previous CT lines (median)	2 (1-6)
BV cycle (median)	6 (1-19)
B symptom	8 (47.1)
Bulky disease	3 (17.6)
Performance (ECOG ≥2)	4 (23.5%)
Previous treatments	
CT	16 (94.1%)
ASCT	1 (5.9%)
Response Rate (ORR)	14 (82.3%)
CR	9 (52.9%)
PR	5 (29.5%)
PD	3 (17.6%)
Cause of Discontinuation	16 (94.1%)
Progression	6 (35.3%)
Bridging to Allo-SCT	1 (5.9%)
Bridging to ASCT	7 (17.6%)
Adverse Event	1 (5.9%)
Death	1 (5.9%)

ASCT: autologous stem cell transplant, BV: brentuximab vedotin, CT: chemotherapy, CR: complete response, ECOG: Eastern Cooperative Oncology Group, ORR: overall response rate, PR: partial response, PD: progressive disease.

Hematological toxicity was observed on 8 (47.1%) occasions. Neutropenia was observed in grades 1-2, thrombocytopenia was variable in grades 1-4. Pneumonia 4 (23.5%), neuropathy 3 (17.6%), renal failure 2 (11.7%), hyperkalemia 2 (11.7%), and infusion reactions 2 (11.7%) were the most seen non-hematological adverse events. BV was stopped in one patient due to adverse events. Other patients did not need dose reduction (Table III).

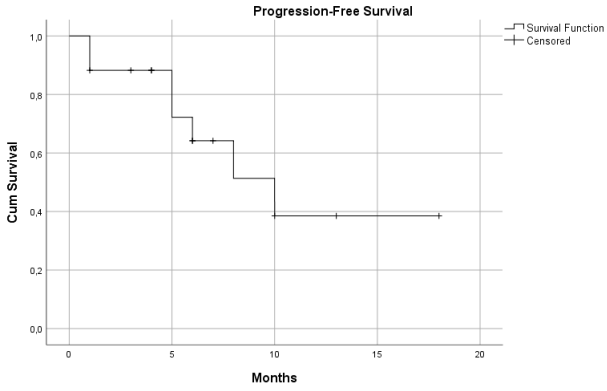
The median PFS of the cohort was 10 months (95% CI, 5.077-14.923). PFS curves are shown in Figure I. Median OS was not reached, and 4 patients deceased in the follow-up period.

Table III. Adverse Events

Adverse Events	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutropenia	3 (17.6%)	1 (5.9%)			
Pneumonia	1 (5.9%)	1 (5.9%)		2 (10.8%)	
Neuropathy	2 (10.8%)		1 (5.9%)		
Hyperkalemia	1 (5.9%)		1 (5.9%)		
Acute renal failure	1 (5.9%)	1 (5.9%)			
Thrombocytopenia	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)	
Infusion reactions			2 (10.8%)		

Common Terminology Criteria for Adverse Events (CTCAE) v5.0 were used for reporting adverse events.

Factors influencing PFS were analyzed, age at diagnosis, gender, clinical data-stage, extranodal disease, subtype, ECOG, received chemotherapy lines, and risk scores did not seem to affect outcome of BV therapy. BV cycle and response to BV therapy were found to affect the PFS; however, in multivariate analysis, no factor was identified to have a significant effect (Table IV).



Median PFS = 10 months (95% CI, 077-14.923)

Figure I: Progression-Free Survival

Table IV. Factors Predicting Progression-Free Survival in Brentuximab Therapy

	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	***p value***	**Odds Ratio (95% CI)**	***p value***
Age at diagnosis	1.011 (0.973-1.050)	*0.586*		
Gender (based female)	1.222 (0.271-5.506)	*0.794*		
The stage at diagnosis (based on early stage)	2.595 (0.432-15.595)	*0.320*		
Extranodal disease at diagnosis (based on none)	0.635 (0.137-2.940)	*0.561*		
BM involvement at diagnosis (based on none)	3.378 (0.401-28.473)	*0.263*		
Subtype (based on PTCL NOS)	1.258 (0.279-5.665)	*0.765*		
Age at BV initiation	1.008 (0.968-1.049)	*0.697*		
Pre-BV CT lines (based ≤2)	0.976 (0.217-4.399)	*0.975*		
BV cycle (based ≤4)	14.401 (1.262-164.377)	*0.032**	4.414 (0.328-59.491)	*0.263*
Pre-BV ECOG (based ECOG 0-1)	0.968 (0.178-5.270)	*0.970*		
Pre-BV bulky disease (based none)	0.554 (0.106-2.980)	*0.484*		
Pre-BV B symptom	0.805 (0.166-3.903)	*0.787*		
Response (based on non-responders)	13.750 (1.430-132.184)	*0.023**	7.057 (0.541-92.053)	*0.136*
SCT (based none)	0.526 (0.101-2.731)	*0.445*		
IPI (based low-intermediate)	0.819 (0.182-3.689)	*0.794*		
AA_IPI (based low-intermediate)	1.379 (0.295-6.450)	*0.683*		
PIT (based group 1-2)	0.867 (0.188-3.991)	*0.854*		
ITLP (based groups 1-2)	1.421 (0.316-6.393)	*0.647*		

*Statically significant

AA_IPI: Age-adjusted International Prognostic Index, BM: bone marrow, BV: brentuximab vedotin, CT: chemotherapy IPI: International Prognostic Index, ECOG: Eastern Cooperative Oncology Group,ITLP: International T cell lymphoma Project, PIT: Prognostic Index for PTCL-U, PTCL-NOS: Peripheral T cell not otherwise specified. SCT: Stem cell transplantation

Discussion

With an observed 82.4% ORR and 52.9 percent CR, our results seem superior to those previously published in the context of patients with recurrent T cell lymphoma receiving chemotherapy. The OS was not reached and the median PFS was 10 months (2). It might not be realistic to draw this comparison

given the lower size of our cohort, but this could be explained by the fact that in our cohort, the patients were not exposed to BV or other targeted novel therapies. In a single-arm trial of 34 patients with recurrent T cell lymphoma treated with BV as a single drug, the response rate we saw seemed to be noticeably higher (ORR and CR within 41% to 82.4% and 24% to 52.9%, respectively) (6). The fact that our sample is younger and had less severe illness may help to explain our findings. After responding to BV treatment, 1 (5.8%) patient received allo-SCT, and 7 (41.1%) patients underwent ASCT, among the eligible patients of our 17 TCLs. Four patients (23.5%) had died during a follow-up of a median of 20 months (range 4-87 months) following the documentation of refractory/relapsed illness. The cohort's median PFS was 10 months (95% CI, 5.077-14.923). The median OS was not attained.

Age at diagnosis, gender, clinical stage, presence of extranodal disease, subtype of TCLs, ECOG performance status, previous chemotherapy history, and prognostic risk scores were not found to influence the outcome of BV therapy. The number of BV cycles and response to BV therapy were found to affect PFS, but no factor was identified as having a significant effect in multivariate analysis.

Although we were unable to define any causes that influence OS, our findings demonstrate the therapeutic importance of achieving CR. Our study had a limitation that our cohort was too small, and we were unable to statistically evaluate the parameters related to PFS or OS.

Neutropenia was observed slightly more than thrombocytopenia. There was no report of neutropenia of grade 3 or higher. One patient had grade 4 thrombocytopenia (5,9%). Pneumonia 4 (23.5%), neuropathy 3 (17.6%), renal failure 2 (11.7%), hyperkalemia 2 (11.7%), and infusion reactions 2 (11.7%) were the most seen non-hematological adverse events. BV was discontinued in one patient due to peripheral neuropathy. Other patients did not need dose reduction. Unlike the previous trials, we did not discover a greater level of toxicity in our entire cohort (6,9,10,11). In contrast, we have fewer peripheral neuropathies. This might be explained by underreporting of these episodes in patients' medical records, a well-known limitation of retrospective investigations. The low prevalence of neuropathies in our sample might be attributed to many of our patients' short-term BV exposure, as peripheral neuropathy is connected to cumulative BV exposure (12).

Conclusion

For orphan diseases due to rare incidence, sometimes it is not feasible to conduct randomized controlled studies, in these conditions real-life reports carry major significance. To the best of our knowledge, our study is the first study that presents real-life experience data for BV.

Our findings support the use of BV monotherapy as a therapeutic option for patients with R/R T-cell lymphomas. Its usage as a monotherapy has been related to an improvement in ORR, making it a feasible choice for young and SCT-naive patients as a bridge to high-dose treatment. The effectiveness of BV in T cell lymphomas, which is an unmet medical need, surely needs more research.

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