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Assessment of the efficiency of Brentuximab Vedotin in patients with pulmonary Hodgkin Lymphoma by the mean of neutrophil to lymphocyte ratio

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ABSTRACT

Background: Lung involvement, an uncommon initial presentation of Hodgkin Lymphoma (HL), may appear as primary or secondary pulmonary HL. Although the combination of Brentuximab vedotin (BV) with AVD is suggested as an alternative treatment to combinations including bleomycin for patients with pulmonary involvement. The efficacy and adverse effects of BV have not been specialized on pulmonary HL. There is insufficient data about neutrophil to lymphocyte ratio (NLR) of cases treated with BV. We performed this retrospective study to evaluate the efficacy and toxicity of BV in patients with pulmonary HL and to demonstrate the prognostic role of NLR in patients treated with BV.

Methods: Data of 10 CD 30 (+) HL patients who treated with BV between years 2011–2016 were analyzed retrospectively. Relapsed cases after autologous bone marrow transplantation (ABMT) and/or resistant cases to at least two lines of chemotherapy, and treated with BV were included in the study.

Results: Patients underwent a median of 8.5 cycles BV. Eight patients (80%) achieved an objective response including 2 of them (20%) with complete response and six of them (60%) with a partial response at the end of the 3rd cycle. At a median follow-up of 16.8 months, median progression-free survival for all patients was 6 months and 3 patients died because of progression. BV, as a single agent, revealed well response in HL cases with pulmonary involvement and other clinical types. No pulmonary toxicity has been occurred due to BV. NLR was found to be o good indicator of prognosis and mortality in pulmonary HL patients and other HL patients. While NLR was not influenced by BV, it can be suggested as an easy prognostic marker in patients treated with BV.

Conclusion: BV may be used as a bridge therapy to the next curative treatment in order to obtain minimal tumor burden in pulmonary HL patients, and NLR can be used as a prognostic marker in these patients. We believe that this study contributes the current literature in terms of being the first research on the referred issue.

1. Introduction

Hodgkin Lymphoma (HL) is a malignant lymphoid neoplasia, characterized by the presence of malignant Hodgkin-Reed Sternberg (HRS) cells.[1] Lung involvement as initial presentation is uncommon for HL (approximately 12%).[2] Lung involvement may present as secondary or primary pulmonary HL. Secondary pulmonary HL is observed in 15–40% of the HL cases, usually, at stages III and IV. On the other hand, primary pulmonary HL is an unusual presentation with less than 100 cases reported worldwide.[3,4] (see Fig. 1)

Multidrug chemotherapy, alone or combined with radiotherapy, provided a curative treatment opportunity in 70–80% of patients.[5]

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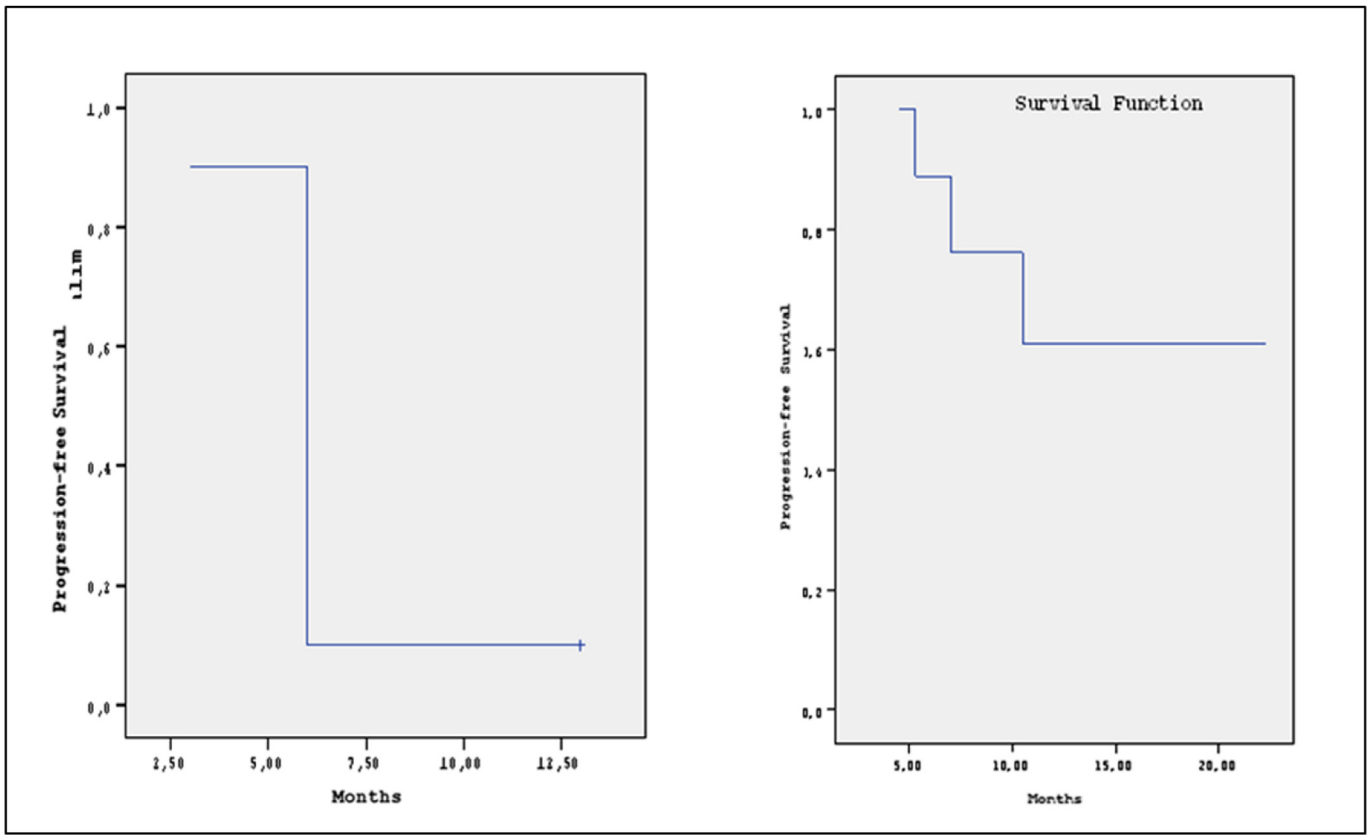

Fig. 1. Progression-free survival and overall survival curves of Brentuximab Vedotin treatment.

Long-term remission cannot be achieved with the conventional treatment options in about 30% of classical HL. The standard treatment approaches for these patients currently are high-dose therapy and autologous bone marrow transplantation (ABMT). BMT provides long-term remission in only 50% of patients.[6]

BV, an antibody-drug conjugate, specifically binds to CD 30 (+) malignant HRS cells and shows tumoricidal effect via a microtubule inhibitor, monomethyl auristatin E (MMAE), that is also structurally built-in.[7] BV - AVD could be an alternative treatment for patients with pulmonary dysfunction in order to avoid the pulmonary adverse effects of bleomycin. Non-infectious pulmonary toxicity including interstitial lung diseases, pneumonitis, and acute respiratory distress syndrome has been reported.[8,9] Nevertheless, the effects and adverse effects of BV have not been specialized on patients with pulmonary involvement.

The International Prognostic Score (IPS) predicts the prognosis of HL patients by the mean of seven prognostic factors. Lymphopenia, which is defined by IPS as less than 600 cells/μL or less than 8% of total white blood cell count have been stated to be associated with poor survival in HL cases.[10] New easier markers are searched. Absolute monocyte count (AMC), absolute lymphocyte count (ALC) and absolute neutrophil count (ANC) had been suggested as significant prognostic factors in HL.[11] In addition neutrophil to lymphocyte ratio (NLR) had been demonstrated to be useful in determining the clinical extent and prognosis in many chronic diseases including HL.[12,13] It has still not been identified whether NLR can be used as a prognostic marker in patients treated with BV or not due to the possible effects of BV on hematological parameters.

We performed this retrospective study considering the lack of data about the outcomes and adverse effects of BV on different extranodal sub-groups of HL and also about the usefulness of NLR in cases treated with BV. We aimed to evaluate the efficacy and toxicity of BV treatment in patients with pulmonary HL in comparison with other HL cases and to demonstrate the role of NLR in patients treated with BV.

2. Material and methods

In this study, data of 10 CD 30 (+) HL patients treated with BV in Medical Oncology Department of Gulhane Health and Education University between August 2011 and January 2016 were analyzed retrospectively. Only the patients treated with BV and relapsed after ABMT or resistant to at least two lines of chemotherapy were included in this study. The study was approved by the local ethics committee of Gulhane School of Medicine. Staging of all patients before BV treatment was performed using PET-CT. Data including the age, gender, age at diagnosis, stage at diagnosis, histopathological type of HL, existence of extranodal involvement, laboratory test results, first-line treatment combination, response to first-line treatment, receiving radiotherapy, time of the first post-treatment relapse, relapse stage, treatment used as salvage therapy, response to salvage treatment, date of ABMT, response to ABMT, date of the post-ABMT recurrence, treatment received after ABMT, stage of the disease before BV treatment, start date, dose, number of cures, response rates and the adverse effects of BV were recorded. The missing data of the patients were completed by contacting the patients.

BV was administered to the patients at a dose of 1.8 mg/kg once every 21 days. Treatment response was assessed at the end of every 3 cycles by FDG PET-CT according to International Working Group response criteria. Toxicity evaluation was performed by the

physician before each treatment, by using Common Terminology Criteria for Adverse Effects of National Health Institutes of America. In this assessment, questions about disease and drug adverse effects were asked, and in the presence of grade 3 toxicity BV dose was reduced to 1.2 mg/kg.

All data were recorded in the computer database and analyzed using SPSS software (SPSS, Inc., Chicago, IL, USA). Results are classified as median, minimum and maximum. Kaplan-Meier method was used for survival evaluation.

3. Results

3.1. Clinical features of the patients before BV

A total of 10 (8 males and 2 females) CD-30 (+) HL patients with a median age of 27.5 years (20–40 years) were included in the study. Demographic characteristics of the patients were shown in Table 1. 8 cases had extranodal involvement of HL. 5 of them had pulmonary involvement and 3 had bone involvement. 2 of the pulmonary HL patients were primary pulmonary HL cases, the remaining 3 patients were secondary pulmonary HL. 2 patients had no extranodal involvement. At the time of initial diagnosis, stage of the patients ranged from 2B to 4B. Bulky disease was observed in two of cases with bone involvement and one of the cases was with no extranodal involvement. ABVD was the first line treatment in all cases. In the first line treatment, complete response was observed in 6 patients, partial response in 2 patients, stable response in 1 patient and progression was observed in 1 patient. Those with partial responses, one case was with secondary pulmonary HL and one case was with no extranodal involvement, and the patient who had stable response was a case with secondary pulmonary HL. No recurrence was observed in cases with bone involvement. Recurrence was observed within an average of 26.2 months in pulmonary HL patients and 31 months in cases with no extranodal involvement. Patients had median of 4 chemotherapy lines (3–5 lines) before treatment of BV except for ABMT, and since the first diagnosis all of the patients underwent radiotherapy at various times. ABMT was performed to 9 of the patients after relapse, and due to the poor ECOG performance status, 1 patient's treatment was initiated with BV without ABMT. The median time to relapse after ABMT was 4[1–19] months and only one case with primary pulmonary HL stayed in remission longer than 12 months after ABMT and had recurred on 19th month. Before the treatment BV, all of the patients were in advanced stages and were refractory to the treatment. The baseline laboratory test results of all cases before the BV treatment were retrieved (Table 2). The mean baseline serum lactate dehydrogenase (LDH) was high in cases with pulmonary involvement, especially in primary pulmonary HL patients (Table 2). Additionally, the mean NLR were higher in pulmonary HL patients than other patients, especially in primary pulmonary HL cases (Table 2). Mean hemoglobin and platelet values were also considerably lower in pulmonary HL patients than others (Table 2).

3.2. BV treatment

The patients received BV treatment for a median of 8.5 cycles[3–16] (9 cycles in cases with pulmonary involvement, 10 cycles in cases with bone involvement and 13.5 cycles in cases with no extranodal involvement).

Objective response rate (complete response rate + partial response rate) was obtained in 8 (80%) patients (3 cases with pulmonary involvement, 3 cases with bone involvement and 2 cases with no extranodal involvement) on 3rd cycle. 20% of these responses were assessed as complete response (one primary and one secondary pulmonary HL patients), 60% were assessed as partial response. Among the remaining secondary pulmonary HL patients with no objective response, one had progression and the other had stable response. In another word, objective response was achieved in all cases with bone involvement and no extranodal involvement. Objective response on 3rd cycle with BV treatment was determined in 60% of pulmonary HL patients. We assessed the laboratory test results after the third cycle. They were substantially similar to the baseline levels (Table 2). Mean serum LDH of pulmonary HL cases was observed to be lower than the baseline level but was still higher than other patients (Table 2). The notable highness of NLR in pulmonary HL cases, especially in primary pulmonary HL patients, was still ongoing. While the mean NLR was 7.39 in all pulmonary HL patients and 10.31 in primary pulmonary HL patients, it was 2.56 in cases with bone involvement and 2.28 in cases with no extranodal involvement (Table 2). The respiratory examination was within normal limits in all patients and emerging respiratory symptoms or findings in terms of pulmonary toxicity were not detected in any of them.

In the post-treatment PET-CT evaluation that performed at the end of 6th cycle, objective response (complete response + partial response) was obtained in 2 (20%) patients (1 case (10%) with secondary pulmonary HL had complete response and 1 case (10%) with bone involvement had partial response). 1 case (10%) with bone involvement had stable response when the remaining 7 patients (70%) had progression. When we evaluated the laboratory test results performed consequently the 6th cycle, we observed that the mean values were approximately similar to those of 3rd cycle (Table 2). The status of NLR was also similar to the results of 3rd cycle. While the mean NLR was 8.08 in all pulmonary HL patients, and 11.64 in primary pulmonary HL patients, it was 2.5 in cases with bone involvement and 2.77 in cases with no extranodal

Table 1
Demographic characteristics of patients.

		Number of patients	%
Age (year)	Median distribution	27.5 (20–40)	
Gender	Male	8	80
	Female	2	20
ECOG	0	0	0
	1	10	100
B – Symptoms		10	100
Response at the last therapy	Complete response	0	0
	Partial response	0	0
	Stable disease	0	0
	Progressive disease	10	100
Number of Patients performed Autologous Bone Marrow Transplantation (Aut.BMT)	9		90
Time Elapsed between Brentuximab Vedotin treatment and Aut.BMT (Months)	23.4 (0.9–55.9)		
Time Elapsed between Initial diagnosis and Brentuximab Vedotin Treatment (Months)	43.9 (17.8–165.3)		

Table 2
Laboratory test results of all cases performed at the initial phase, end of 3rd cure and end of 6th cure.

		All patients (n = 10)	Pulmonary involvement (n = 5)	Bone involvement (n = 3)	No extranodal involvement (n = 2)
Baseline results	WBC(x 10^3/μL)	8700	11840	5600	5500
	Hgb(g/dL)	11.04	9.10	12.73	13.35
	Plt (x 10^3/μL)	176400	94200	263333	251500
	#neutrophil (x 10^3/μL)	5680	8460	3000	2750
	#lymphocyte (x 10^3/μL)	1220	1270	1166	1175
	NLR	5.14	*7.71*	2.63	2.45
	LDH(U/L)	358.8	617.2	116.6	76
3rd cure results	WBC(x 10^3/μL)	8120	10880	5333	5400
	Hgb(g/dL)	11.98	11.58	11.86	13.15
	Plt (x 10^3/μL)	176400	125200	216666	244000
	#neutrophil (x 10^3/μL)	5290	8140	2500	2350
	#lymphocyte (x 10^3/μL)	1175	1330	1000	1050
	NLR	4.66	*7.39*	2.56	2.28
	LDH(U/L)	235.1	348.4	96.66	159.5
6th cure results	WBC(x 10^3/μL)	7420	9820	4966	5100
	Hgb(g/dL)	12.37	12.18	11.63	13.95
	Plt (x 10^3/μL)	229400	221200	233333	244000
	#neutrophil (x 10^3/μL)	5041	7720	2370	2350
	#lymphocyte (x 10^3/μL)	1099	1200	996	1000
	NLR	5.09	*8.08*	2.5	2.77
	LDH(U/L)	228.9	334.8	112.6	138.5

WBC: white blood cell, Hgb: hemoglobin, Plt: platelet, NLR: neutrophil to lymphocyte ratio, LDH: lactate dehydrogenase.

involvement (Table 2). Respiratory examination was still within normal limits in all patients at this phase and emerging respiratory symptoms or findings in terms of pulmonary toxicity were also not detected in any patient.

Lastly, in the post-treatment PET-CT evaluation of 9th cycle, complete response was obtained in only 1 (10%) case with secondary pulmonary HL. 1 patient (10%) with bone involvement who had stable response on the 6th cycle had stable response again. The remaining 8 patients (80%) had progression. All of the patients were still free of emerging symptom or finding in terms of pulmonary toxicity at this phase. Overall assessment of laboratory test results revealed that BV did not influence the usefulness of NLR.

3.3. Post-treatment findings

Allogeneic BMT was performed in 7 cases. All cases underwent low-intensity conditioning regimen following allogeneic BMT. 6 of the Allogeneic BMT were haploidentical due to the lack of suitable donor, and the other one was transplanted from the full matched sibling. During the follow-up period of 16.8 (4.7–22.8) months, median progression-free survival was determined as 6 months; and 3 patients died within the first 6 months depending on the progression of the disease after treatment. The overall mortality rate was 60%. All cases with pulmonary involvement had died. Survival group was consisting of two patients with bone involvement and two patients with no extranodal involvement. The patients without extranodal involvement seemed to have a better prognosis. Pulmonary HL patients whose mean NLR values were higher were exactly opposite. The average of NLR results of all cases showed notable difference between survival and death groups. The average value of all calculated NLR levels of 0th, 3th, 6th cycles was 2.36 in survival group and it was 6.94 in death group.

3.4. Adverse effects

No interruption or suspension occurred due to the toxicity of BV treatment including pulmonary and hematological adverse effects in any of the patients. On 3rd cycle, grade 3 peripheral motor neuropathy-related dose reduction was made in only one patient who did not have myelotoxicity that require transfusion or G-CSF use. The incidences of grade 3 neutropenia and thrombocytopenia were 20% and 10% respectively. Neither G-CSF nor platelet transfusion were used in any of our neutropenic or thrombocytopenic patient for therapeutic or prophylactic purposes. Peripheral sensory neuropathy (70%), weakness (80%), nausea (60%), vomiting (60%), loss of appetite (40%), abdominal pain (60%), weight loss (40%), headaches (60%), diarrhea (10%), fever (10%), alopecia (30%), myalgia 40%) and insomnia (30%) were observed in patients at the frequency specified in brackets (Table 3). There was no significant difference between extranodal involvement groups in terms of adverse effects.

Briefly, BV, as a single agent, revealed well response in HL cases with pulmonary involvement and other clinical types. No pulmonary toxicity has been occurred due to BV. NLR was found to be o good indicator of prognosis and mortality in pulmonary HL patients and other HL patients. However NLR was not influenced by BV, it can be suggested as an easy prognostic marker in patients treated with BV.

4. Discussion

In this study, data of 10 CD 30 (+) HL patients treated with BV in a single center were analyzed retrospectively. The efficiency of BV was assessed by the mean of NLR and a comparison was made between pulmonary HL cases and other extranodal conditions of

Table 3
Side effects of brentuximab vedotin treatment.

Side effects	All Grades		Grade 3		Grade 4	
	n	%	n	%	n	%
Peripheral sensory neuropathy	7	70	1	10	0	0
Nausea	6	60	1	10	0	0
Fatigue	7	70	0	0	0	0
Neutropenia	2	20	0	0	0	0
Diarrhea	1	10	0	0	0	0
Fever	2	20	0	0	0	0
Vomiting	6	60	0	0	0	0
Arthralgia	5	50	1	10	0	0
Itching	2	20	0	0	0	0
Myalgia	4	40	0	0	0	0
Peripheral motor neuropathy	1	10	1	10	0	0
Alopecia	3	30	0	0	0	0

the disease. Considering that the patients in our cohort had received a median of 4 chemotherapy lines before BV. 7 of the patients underwent allogeneic BMT, and all were resistant to the last chemotherapy they had received. It can be stated that the response to BV as a single agent was pretty good. In terms of objective response, our study contains similar results at early stage (80% vs. 75%) when compared with the phase II study of Younes et al. consisting of 102 patients.[14] However, the fact that the rate of objective response decreased to 10% in PET/CT assessment performed post-treatment on 6 cycles of BV. The progression was observed in 7 patients who had partial response in the early stages, suggest that the treatment of BV is insufficient to achieve long-term remission. In fact, the following decrease in high objective response rates achieved in the first three cycles of BV treatment supports our hypothesis.[14–16] In the phase II study of Younes et al. the initial 40% partial response rate decreased to %36 after 3rd cycle and 13% after 6th cycle.[14] At the end of 6th cycle, it was observed that only 1 of the 22 patients could maintain his/her stable state, and the remaining 21 patients had disease progression. Median progression-free survival of 21.5 months was observed in patients with complete response supports our data, while it was 5.1 and 3.5 months, respectively in patients with partial response and stable cases.

The lack of achieving long-term remission seems to be the weakest feature of BV treatment. But, it shouldn't be forgotten that this drug, alone, can achieve the response in patients who previously had intensive treatment and ABMT. In patients who had relapsed after ABMT, BV seems to be a more effective and better-tolerated treatment option, compared with the CALGB (gemcitabine, vinorelbine and pegylated liposomal Doxorubicin have been used) study.[17] In the CALGB study of gemcitabine, vinorelbine and pegylated liposomal doxorubicin, objective response obtained as 75% and only 17% of that response was complete response. However, complete response rate obtained after 3rd cycle was 20% in our study and 34% in the phase II study of Younes et al.[14]

When we evaluate our study together with the other three studies, it's observed that achieving long-term remission seems to be difficult in the group of patients who couldn't obtain complete response by BV.[14–16] There is certainly a need of another consolidation therapy to cure this group of patients. This treatment can be allogeneic BMT or other drugs used in clinical trials.[18–22] In a prospective study by Chen at al., after a median of 12.4 months follow-up of 14 HL patients who had been treated with BV and performed Allogeneic BMT afterward, 1-year overall survival and the progression-free survival rates were reported as 100% and 92.3%, respectively.[9]

The results of our study have shown that BV is a quite convenient treatment option, in terms of toxicity. In the CALGB study, grade 3–4 neutropenia, thrombocytopenia and febrile neutropenia developed in 51%, 43%, 11% of the patients, respectively. In our study, febrile neutropenia had never been observed, and the incidences of grade 3 neutropenia and thrombocytopenia were 20% and 10% respectively.[17] Such a low myelosuppressive effect observed in patients who are previously treated with chemotherapy and radiotherapy (both have negative effects on bone marrow reserves), seems to be a significant advantage of BV. On the other hand, usefulness of NLR as a prognostic marker in HL had also been demonstrated in previous studies.[12] However, its accuracy has not been assessed in patients treated with BV. Therefore, we think that our study contributes new data to the current literature also about the role of NLR in HL cases treated with BV. We observed that NLR is a good marker for prognosis and mortality, and does not influenced by BV treatment. Pulmonary toxicity, which had been previously reported as an important adverse effect of BV, was not observed in any of our cases including the patients with pulmonary HL.[8] However non-infectious pulmonary toxicity has been reported previously, we have not met any study focusing on the efficacy of BV on extranodal involvements of HL, especially primary pulmonary HL. Associated to this point, Petrini et al. reported a 22-year-old male case with cystic fibrosis and emerging HL with diffuse localizations.[23] They had adopted a modified ABVD schedule with BV instead of bleomycin because of the risk of pulmonary toxicity by the use of the standard treatment, ABVD, and radiotherapy. They reported that the patient was in complete remission without any impairments of lung function after 15 months of the BV treatment. They stated that the use BV-AVD schedule is suggestible in patients with lung diseases for whom bleomycin toxicity should be harmful.

Additionally, adverse effects such as peripheral sensory neuropathy, muscle pain, joint pain, fever, malaise, nausea, vomiting, abdominal pain and loss of appetite were observed in our patients in order of frequency. These adverse effects were similar to the literature.[24] Because the adverse effects were mostly grade 1–2 level and could be treated by supportive approaches, neither dose reduction nor dose suspension needed in patients, except 1 patient who developed peripheral motor neuropathy. For that patient who underwent dose reduction, motor neuropathy decreased to grade 1 level in 3 months follow-up.

This study is a retrospective evaluation of patient's data from a single center. Therefore, it contains the limitations inherent in any retrospective study. Although the small number of patients may seem like a limitation, it's more accurate efficacy and toxicity sampling than the phase studies is an advantage. Considering the indications of BV, it is very difficult for a single-center to achieve a large number of patients in a short time. Therefore, better understanding the role of BV in terms of efficacy and toxicity in treatment of pulmonary and other extranodal involvement of HL depends on performing multi-centered studies at national scale. We believe that this study contributes the current literature in terms of being the first research about the effects and adverse effects of BV on patients with pulmonary HL in comparison with other extranodal involvement subtypes, and also about the usefulness of NLR in patients treated with BV.

Conflicts of interest

The authors declare no conflicts of interest.

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