

Role of Brentuximab vedotin along With Chemotherapy in Patients with CD30 Antigen Positive Aggressive Lymphomas: Single Centre Experience from a Developing Country

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Abstract

Objective: To evaluate the effectiveness and safety of brentuximab vedotin in managing Hodgkin's lymphoma and anaplastic large cell lymphoma in patients with histologically proven aggressive CD30 antigen lymphoma on biopsy.

Method: The retrospective study was conducted at the Department of Clinical Haematology and Bone Marrow Transplant, Dow University of Health Sciences, Ojha Campus, Karachi, and comprised data from March 1, 2020, to March 31, 2023, of patients with Hodgkin's lymphoma and anaplastic large cell lymphoma who received brentuximab vedotin at 1.8mg/kg intravenous every three week along with chemotherapy. The assessment of the response was conducted using the Lugano criteria of 18F-fluorodeoxyglucose positron emission tomography/computed tomography. The primary endpoint was overall response rate, which included complete metabolic response and partial metabolic response. Data was analysed using SPSS 26.

Results: Of the 24 patients with median age 24.50 years (Interquartile range: 18-32 years), 14(58.3%) were male, 10(41.7%) were females, 17(70.8%) had complete metabolic response, 6(25%) had progressive disease, 1(4.2%) had partial metabolic response, 5(20.8%) were given three cycles of brentuximab vedotin and bendamustine, and 3(12.5%) were treated with six cycles of brentuximab vedotin and bendamustine. Of the patients with complete metabolic response, autologous bone marrow transplant was done in 11(64.7%).

Conclusion: Brentuximab vedotin in combination with chemotherapy was found to be an effective and safe treatment option for CD30 antigen positive lymphoproliferative disorders.

Keywords: Hodgkin's lymphoma, Anaplastic large cell lymphoma, Brentuximab vedotin, Bendamustine.

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Introduction

Cytotoxic agents have been able to specifically target cancer cells with the development of monoclonal antibodies, resulting in a long-lasting anti-cancer immune response, which is the primary goal of treating malignant tumours. Cancer therapy now relies on monoclonal antibody-based chemo-immunotherapy combinations.¹ Monoclonal antibodies against cluster of differentiation-30 (CD30) antigen can be used to target cancer cells in lymphomas like Hodgkin's lymphoma (HL) and anaplastic large cell lymphoma (ALCL), which express CD30 antigen.

Brentuximab vedotin (BV) is an anti-CD30 monoclonal antibody conjugated with cytotoxic agent monomethyl

auristatin E. BV with chemotherapy has demonstrated significant clinical benefits and acceptable tolerability in clinical trials and was approved in 2011 by the United States Food and Drug Administration (FDA) for use in HL and ALCL.² Although the rate of cure is high for HL, approximately 5-10% cases fail to respond to adriamycin (doxorubicin)+bleomycin+vinblastine+dacarbazine (ABVD) regime, and recurrence is noted in approximately 10-30% cases after achieving an initial response. Salvage chemotherapy is the first step in treating relapsed HL, followed by autologous bone marrow transplantation. Treatment outcomes are significantly influenced by the disease status at the time of transplantation.³

Studies have extensively evaluated the benefit of adding BV with routine salvage chemotherapy, including ifosfamide+carboplatin+etoposide (ICE), etoposide+methylprednisolone+high-dose cytarabine_cisplatin (ESHAP) and dexamethasone+high-dose cytarabine+cisplatin (DHAP). BV-based combinations are promising in terms of their higher complete remission rates than chemotherapy alone.⁴ However, significant complications are associated with these salvage regimens and the risk of grade 3-4 toxicities is 57.1% with ICE and 43-48% with

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DHAP.^{5,6}

The combination regimen of BV and bendamustine (BvB) has emerged as a highly effective option with a favourable toxicology profile. The first study which evaluated BvB in refractory and relapsed HL comprised 55 patients, of whom 39(73.6%) achieved complete response. Infusion-related reactions and peripheral neuropathy were the most common side-effects, which were manageable in most patients. Most interestingly, there was no episode of febrile neutropenia, and majority of the patients on this regimen were followed on an outpatient basis compared to the routine salvage regimes that require hospital stay, making it a preferred treatment option in many haematological centers.⁷

Combining BV with chemotherapy is also effective in treating CD30-positive T-cell lymphomas. A study assessed the effectiveness of BV on untreated patients with CD30-positive peripheral T cell lymphoma (PTCL). Patients were randomised to receive BV+cyclophosphamide+doxorubicin+prednisone (B-CHP) or cyclophosphamide+doxorubicin+vincristine+prednisone (CHOP). The response rate and overall survival (OS) of the B-CHP group were significantly improved, and the side-effects were comparable between the groups.⁸

Frequencies of histological types of lymphoma in Pakistani population were published in 2015. Of the 318 lymphoma cases, 79(25%) were diagnosed as HL, while ALCL was the most common T-cell subtype, accounting for 10(4.2%) cases.⁹ Another study in Pakistan included 300 cases, and 76(25.3%) of them had HL, while 6(2.6%) had ALCL.¹⁰

To our knowledge, no data has been published so far regarding the evaluation of BV along with chemotherapy in the Pakistani population. The current study was planned to fill the gap in literature by evaluating the overall response rate and safety profile of BV and chemotherapy in managing HL and ALCL in patients with histologically proven aggressive CD30 antigen lymphoma on biopsy.

Materials and Methods

The retrospective study was conducted at the Department of Clinical Haematology and Bone Marrow Transplant, Dow University of Health Sciences (DUHS), Ojha Campus, Karachi, and comprised data from March 1, 2020, to March 31, 2023. Data was retrieved using a predesigned proforma after approval from the institutional ethics review board.

Data was retrieved for all patients admitted with histologically proven aggressive CD30 antigen lymphoma on biopsy of a lymph node or extra nodal mass as per the World Health Organisation (WHO) 2016 classification.¹¹ No formal sample size calculation was done because of the

study's retrospective design. All eligible patients of either gender aged 15-65 years with a diagnosis of CD30 antigen-positive lymphoma who received BV-based therapy were included. Biopsy for confirmation of relapsed/refractory disease had been done in all the patients.

Those excluded were medically unfit patients and those with incomplete records. Patients with uncontrolled comorbid conditions, such as advanced cardiovascular, renal, hepatic or pulmonary disease, or uncontrolled diabetes, were also excluded because such conditions could significantly influence both the tolerability and safety of BV-based chemotherapy.

BV 1.8mg/kg was administered intravenously (IV) along with chemotherapy every three weeks for 2-6 cycles. The selection of a combination chemotherapy regimen was individualised and made at the discretion of the attending physician, taking into account each patient's clinical condition, prior treatment history, disease status (relapsed, refractory or upfront), and lymphoma subtype, to optimise therapeutic benefit and to minimise toxicity.

The applied treatment regimens included BvB (BV 1.8mg/kg on day 1 and bendamustine 90mg/m² on days 1-2),¹² BV-CHP (BV 1.8mg/kg on day 1, cyclophosphamide 750mg/m² on day 1, doxorubicin 50mg/m² on day 1, prednisolone 100mg daily for 5 days),¹³ G-BV (BV 1.8 mg/kg on day 1 and gemcitabine 1,000mg/m² on days 1 and 8).¹⁴ Most relapsed HL patients were given BvB combination. None of the patients in the cohort received lenalidomide or rituximab in combination with BV.

The assessment of the response was conducted using the Lugano criteria of 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT).¹⁵ The primary endpoint was overall response rate (ORR), which included complete metabolic response (CMR) and partial metabolic response (PMR).

The PET/CT scan involved the administration of radioactive FDG-18 sugar, and then the CT scan took images of the body at various angles. Cancer cells were the rapidly dividing cells, and they needed more energy than the normal healthy tissues. PET/CT scans detected cancer cells as areas with increased absorption of radioactive glucose.¹⁵

The PET/CT scans were interpreted using the Deauville five-point scale, which ranges from 1 = the best response and 5 = the worst response,¹⁶ with 1 =absence of uptake; 2 = some uptake, but less than or equal to mediastinum blood pool; 3 = uptake more than mediastinum, but less than or equal to uptake of liver; 4 = high uptake more than liver; and 5 = very high uptake or development of new areas of uptake that were not present previously. Further, score 1-3

indicated CMR, while score 4-5 indicated PMR.

The PET/CT scan was done at baseline, and was repeated after 2-3 treatment cycles. CMR and PMR patients were given 1-2 more cycles, while patients with lack of response or progressive disease (PD) underwent change in the treatment regimen.

Data was analysed using SPSS 26. Median and interquartile range (IQR) were calculated for quantitative variables, while frequencies and percentages were reported for qualitative variables. Associations between response and clinical variables were explored using simple cross-tabulations, and Fisher's exact test was applied, where appropriate, to see the effect of risk factors on outcome. $P < 0.05$ was considered significant.

Results

Of the 24 patients with median age 24.50 years (IQR: 18-32 years), 14(58.3%) were male, 10(41.7%) were females. Of the total, 19(79.2%) patients were aged < 35 years. There were 21(87.5%) patients with HL and 3(12.5%) with ALCL. Among the HL cases, 20(95.2%) were relapsed/refractory cases and 1(4.8%) patient was given treatment in upfront setting. Among the ALCL cases, 1(33%) patient had relapsed disease, whereas 2(67%) were initial patients. Overall, 17(70.8%) patients achieved CMR, 6(25%) had PD, 1(4.2%) could achieve PMR, 5(20.8%) were given three cycles of BvB, and 3(12.5%) were treated with six BvB cycles (Table 1). Of the patients with CMR, autologous bone marrow transplant was done in 11(64.7%) cases. Out of the total, 22(91.7%) patients had a history of previous treatment. Also, 8(36.4%) patients had received 1st line treatment, 12(54.5%) had received 2nd line treatment, and 2(9.1%) had received 3rd line treatment. One (4.2%) patient had

Table-1: Treatment regimens with BV-based combinations. (n=24).

	n (%)
Brentuximab vedotin + chemo cycles	
2 cycles BvB	4(16.7)
2 cycles BvB & 2 cycles G-BV	2(8.3)
3 cycles BvB	5(20.8)
3 cycles BvB, 2 cycles BVD	1(4.2)
4 cycles BvB	2(8.3)
4 cycles BvB & 2 cycles brentuximab	1(4.2)
5 cycles BvB	2(8.3)
6 cycles BvB	3(12.5)
6 cycles Bv-CHP	1(4.2)
6 cycles BvB, 2 cycles of brentuximab	1(4.2)
Response	
Complete Metabolic Response	17(70.8)
Progressive disease	6(25)
Partial Metabolic Response	1(4.2)

BV: Brentuximab vedotin, BvB: Brentuximab vedotin+bendamustine, G-BV: Brentuximab vedotin+gemcitabine, Bv-CHP: Brentuximab vedotin+cyclophosphamide+doxorubicin+prednisolone, BVD: Brentuximab vedotin+vinblastine+dacarbazine.

Table-2: History of previous treatment protocol.

Past Treatment protocol	Number of Past Treatment Lines		
	1st Line	2nd Line	3rd Line
ABVD	5	0	0
CHOP	2	0	0
ISRT	1	0	0
ABVD & DHAP	0	8	0
CHOP & ICE	0	1	0
COPD/ABVD & EPIC	0	3	0
CHOP, DHAP, BEGEV	0	0	1
COPD/ABVD, EPIC, DHAP	0	0	1
Total	8	12	2

CHOP: Cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate and prednisone, ABVD: Doxorubicin hydrochloride, bleomycin, vinblastine sulfate and dacarbazine, DHAP: Dexamethasone, high-dose cytarabine, cisplatin, ICE: Ifosfamide, carboplatin, etoposide, BEGEV: Gemcitabine, prednisolone, vinorelbine, bendamustine, EPIC: Etoposide, prednisolone, ifosfamide and cisplatin, ISRT: Involved site radiation therapy.

Table-3: Frequency and association of response according to demographic and clinical factors.

	Response [n (%)]			p-value
	Complete Response	Progressive Disease	Partial Response	
Gender				
Male	10(58.8)	3(50)	1(100)	<0.999
Female	7(41.2)	3(50)	0(0)	
Age Groups				
≤35 years	12(70.6)	6(100)	1(100)	0.424
>35 years	5(29.4)	0(0)	0(0)	
Diagnosis				
ALCL	1(5.9)	0(0)	0(0)	0.595
HL	1(5.9)	0(0)	0(0)	
Refractory ALCL	1(5.9)	0(0)	0(0)	
Refractory HL	6(35.3)	5(83.3)	0(0)	
Relapsed ALCL	1(5.9)	0(0)	0(0)	
Relapsed HL	7(41.2)	1(16.7)	1(100)	
Past treatment				
Yes	15(88.2)	6(100)	1(100)	<0.999
No	2(11.8)	0(0)	0(0)	
Past treatment Lines (n=22)				
1 Line	7(46.7)	1(16.7)	0(0)	0.129
2 Lines	7(46.7)	5(83.3)	0(0)	
3 Lines	1(6.7)	0(0)	1(100)	
BV + chemo cycles				
2 cycles BvB	1(5.9)	3(50)	0(0)	0.035*
2 cycles BvB & 2 cycles G-BV	0(0)	2(33.3)	0(0)	
3 cycles BvB	5(29.4)	0(0)	0(0)	
3 cycles BvB, 2 cycles BVD	1(5.9)	0(0)	0(0)	
4 cycles BvB	3(17.6)	1(16.7)	0(0)	
4 cycles BvB & 2 cycles brentuximab	1(5.9)	0(0)	0(0)	
5 cycles BvB	1(5.9)	0(0)	1(100)	
6 cycles BvB	3(17.6)	0(0)	0(0)	
6 cycles Bv-CHP	1(5.9)	0(0)	0(0)	
6 cycles BvB, 2 cycles of brentuximab	1(5.9)	0(0)	0(0)	

ALCL: Anaplastic large cell lymphoma, HL: Hodgkin lymphoma, BV: Brentuximab vedotin, BvB: Brentuximab vedotin+bendamustine, G-BV: Brentuximab vedotin+gemcitabine, Bv-CHP: Brentuximab vedotin+cyclophosphamide+doxorubicin+prednisolone, BVD: Brentuximab vedotin+vinblastine+dacarbazine. Fisher Exact test was applied. *Significant at 0.05 level.

previously received involved-site radiation therapy (ISRT) as part of initial or salvage treatment protocol (Table 2).

Age, gender, diagnosis, history and mode of past treatment were not significantly associated with outcomes ($p>0.05$), but there was a significant association of response with BV+chemotherapy cycles ($p=0.035$) (Table 3).

Overall, the treatment was well tolerated with no significant side-effects. There were 2(8.3%) patients with grade II neutropenia; 1(50%) had ALCL and received treatment with B-CHP, and 1(50%) had refractory HL who had PD on BvB, and was given G-BV. The patient expired after the 2nd cycle of G-BV due to sepsis.

Also, there was one ALCL patient who had been treated with B-CHP in upfront setting, but expired after the 2nd cycle due to sepsis, and, hence, was excluded from the study.

Among the patients included, 1(4.2%) patient had tuberculosis (TB) activation during treatment, which was diagnosed on the bronchoalveolar lavage and acid-fast bacillus (AFB) geneXpert. The patient improved with anti-TB therapy and became asymptomatic.

None of the patients experienced peripheral neuropathy or reactions related to infusion. There was no episode of grade III/IV neutropenia in the patients who received BvB.

Discussion

Clinically significant benefits have been demonstrated in vitro and in clinical trials for the treatment of HL and other CD30 antigen positive lymphoproliferative disorders with BV, an antibody-drug conjugate that targets CD30.¹⁷

The CD30 antigen is a member of tumour necrosis factor (TNF) family, and its ability to influence the development and survival of malignant lymphoma cells may depend on the signalling cell type and environment, or may enhance anti-proliferation and lead to cell death. Interleukin-6 (IL6) and TNF-alpha are among the inflammatory cytokines upregulated by the CD30 receptor in HL. It also enhances the expression of adhesion molecule-1 on Reed-Sternberg (RS) cells. Monoclonal antibodies against CD30 antigen are therapeutic because RS cells in HL and ALCL cells express it.¹⁸

The inclusion of both classical HL (cHL) and ALCL in this study was deliberate, as both entities share a common biological characteristic of CD30 antigen expression, which serves as the therapeutic target of BV. In 2011, the first phase-II pivotal multicentre trial, which led to approval of BV, included 102 cases of relapsed and refractory HL after an autologous bone marrow transplant. A reduction in

lymphoma burden was observed in approximately 97% of the patients, with objective response in 75% and complete response in 34%. The overall response rate and progression-free survival (PFS) were 41% and 21%, respectively, at the end of five years.¹⁹ The first study which evaluated the safety and efficacy of BV in relapsed and refractory ALCL was done by Barbara Pro, et al.²⁰ This multicentre phase-II enrolled patients from June 2009 to May 2010. BV 1.8mg/kg was given for up to 12 cycles. An overall response rate of 86% was reported by the investigators, with 66% of respondents giving complete responses. Patients who responded fully had a better outcome with 79% OS and 57% PFS, even though the five-year survival rate was 60%. BV demonstrated a good safety profile and tolerance, and the commonest complication was peripheral neuropathy (57%). On follow-up, there was response or improvement in peripheral neuropathy in 91% patients.²⁰

The incorporation of BV into routine cytotoxic agents has led to a significant improvement in the management of relapsed and refractory CD30 antigen-positive lymphoma. To achieve full remission before undergoing an autologous bone marrow transplant is the primary goal of relapsed and refractory lymphoma. The most common salvage treatment options are ICE and DHAP which have a complete remission rate of around 21-26%. Gemcitabine+vinorelbine+liposomal doxorubicin (GVD) has a CMR rate of 19%. More intensive cytotoxic agents, like ifosfamide+gemcitabine+vinorelbine+prednisolone (IGEV) & ESHAP, despite better complete remission rates of 54% and 50%, respectively, failed to show PFS benefits. BV can be used as a monotherapy, or in combination with chemotherapy to treat HL. A phase-II study evaluated BV with ICE. The patients were administered two cycles of BV monotherapy, 28% patients with CMR were proceeded directly with autologous bone marrow transplant. Patients with less than partial response received ICE chemotherapy prior to autologous stem cell transplantation. The complete response and objective response rate for BV monotherapy were 28% and 73%, for BV+DHAP 78% and 87%, and for BV+nivolumab 67% and 85%, respectively.²¹

The BvB combination has become a successful chemotherapy regimen with excellent tolerance. the regimen was analysed by the Austrian Study Group for Medical Tumour Therapy (AGMT) for efficiency and safety. The study included 28 patients of cHL and 5 patients with PTCL. Most of the patients had a good performance status and had previously received at least one treatment regimen. One patient of chronic lymphocytic leukaemia with Richter's transformation into HL was also included in that study, and the patient was given BV 1.8 mg/kg on day

1 and bendamustine 70-90mg/m² on days 1-2 every 3 weeks. Overall, 22(78.6%) patients achieved a complete response and 6(21.4%) achieved a partial response. Of the 24 patients of relapsed and refractory HL in a study, 75% had complete response and 25% had partial response. Although the combination was generally safe, a few patients experienced mild to moderate adverse events. The commonly noted side effects were peripheral neuropathy (10.7%), infusion reactions (35.7%) and infections requiring treatment (35.7%). Three patients had severe neutropenia during treatment and were given granulocyte colony-stimulating factor (G-CSF).¹² Another retrospective study was conducted to evaluate the outcomes of BvB in 16 patients with relapsed and refractory HL. Overall, it was found that the response rate was 80%, and 50% of patients had complete response.²² Clinical outcomes on long-term follow-up of patients treated with BvB were published by Moretti M et al.²³ The median PFS for all patients with HL treated with BvB was 26 months after a 38-month follow-up. The complete response rate was 50%, with no significant association with previous number of chemotherapy treatment lines, relapsed and refractory lymphoma. No grade IV or any new adverse event were observed during this period. Based on the authors' conclusion BvB was an effective and safe salvage treatment option for patients with HL.

These studies demonstrated clinically significant benefits of adding BV with routine chemotherapy in relapsed and refractory HL cases. Studies were also conducted to see the role of BV in the upfront treatment of HL. A trial evaluated the outcome of adding BV to chemotherapy in advance-stage cHL. The patients were randomised to receive six cycles of Adcetris (BV)+adriamycin (doxorubicin)+vinblastine_dacarbazine (A+AVD) or ABVD. Updated analysis favoured OS benefit. The estimated OS rate and PFS in the A-AVD group was 93.9% and 82.3% and 89.4% and 74.5% in the ABVD group at six years. The safety profile was comparable in both the groups. Most patients in both the groups had a continuous improvement in peripheral neuropathy. Incidence of second malignancies was less in the A+AVD group compared to the ABVD group (23 vs 32). The rates of successful pregnancies were better in females who received A+AVD compared to ABVD (49 vs 28).²⁴

The primary objective of the current study was to evaluate the efficacy and safety of BV in Pakistani population. The retrospective study included 21 patients of HL, and, of them, 20 had relapsed and refractory lymphoma. One female patient was treated upfront, she had stage III extra nodal and bulky disease with history of postpartum dilated cardiomyopathy and ejection fraction (EF) of 30-35%. She had CMR after three cycles of BvB. She was given a further

three cycles of brentuximab+vinblastine+dacarbazine.

All relapsed and refractory cases received treatment with BvB combination. Out of them, 13(65%) patients had complete response documented by PET CT scan. Most patients needed >2 cycles of BvB. Additionally, six patients had disease progression on BvB, and two of them were further treated with G-BV, but still failed to respond. One patient had a partial response after two cycles of BvB, but PET CT scan after four cycles showed PD. One PD patient was given IGEV, and post-treatment the patient had grade IV neutropenia and septic shock, remained admitted in intensive care unit (ICU) and then refused further treatment and was lost to follow-up. One PD case was switched to nivolumab, with lack of response after four cycles. One patient had relapsed HL after an autologous bone marrow transplant, had previously received three lines of chemotherapy. He had partial response with BvB, and was planned for allogeneic bone marrow transplant, but there was no suitable matching donor.

Most of the patients were given BvB on a daycare basis, except a few patients coming from other cities.

Of the 13 patients who had CMR with BvB, autologous bone marrow transplant was done in 11 patients. While one patient did not agree for autologous bone marrow transplant, one female patient had grade III-IV radiation pneumonitis with markedly reduced diffusing capacity of the lungs for carbon monoxide (DLCO). Her condition improved with steroids, but she was not stable enough for an autologous bone marrow transplant. Out of the 11 patients who underwent autologous bone marrow transplant, one patient expired with neutropenic sepsis during transplant, and 10 patients were discharged after successful autologous bone marrow transplant.

A trial showed improved outcome of adding BV to chemotherapy. The phase-III study included 452 patients from 17 countries. Most patients had ALCL (70%). The patients were randomised to receive 6-8 cycles of A-CHP (Adcetris also called Brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone) and CHOP. The 5-year follow up showed PFS 51.4% (42.8-59.4%) with A+CHP versus 43% (35.8-50%) with CHOP. The OS rates were 70.1% with A+CHP and 61% with CHOP. Interestingly re-treatment with BV in relapsed patients still showed an objective response of 59%.²⁵

The current study included 4 patients of ALCL. One patient expired after the 2nd cycle of B-CHP, and his response evaluation was not done, so he was not included in the study. One patient had chronic liver disease, so he was given a single-agent BV. One patient of relapsed ALCL was

given BvB, the other patient was treated with B-CHP in upfront setting. All three patients of ALCL had CMR.

Overall treatment was well tolerated with manageable toxicity in majority of the current patients, and one interesting finding in the study is lesser incidence of peripheral neuropathy and infusion reactions compared to those reported in literature.^{26,27}

The current study has limitation of a retrospective design, a small sample size, and the lack of a control group. As such, the results should be interpreted as exploratory and hypothesis-generating rather than confirmatory. Another important limitation was the unavailability of complete stage-wise disease documentation in all the patients, which prevented stage-based outcome stratification. Additionally, patients in the study had cancer at different stages. This heterogeneity may influence treatment response and could limit the ability to clearly attribute the observed outcomes to the effect of the drug. Finally, one possible explanation of lower incidence of adverse reactions in the study is the younger age of the patients. Large patient groups and long-term follow-up are needed to validate the current findings.

Conclusion

BV+chemotherapy was generally well-tolerated, with only 12.5% patients experiencing notable adverse effects. The combination was found to be an effective and safe treatment option for CD30 antigen-positive lymphoproliferative disorders.

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Author Contribution:

DS & FAK: Design, data collection and writing.

SK: Data analysis and collection.

FQ & NA: Data analysis and results compilation.

AP: Data analysis and results.