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Research Article

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Outcomes of Brentuximab Vedotin with or without Bendamustine and Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma: An Early Experience from Patient Access Programme in India

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Abstract

Hodgkin's lymphoma (HL) accounts for 30 % of all lymphomas. The primary therapy regimens ABVD or BEACOPP are frequently used for Hodgkin's lymphoma. Up to 40% of patients with advanced Hodgkin's Lymphoma (HL) experience a relapse after receiving their first therapy, despite current treatment protocols. Autologous Stem Cell Transplantation (ASCT) can produce long-lasting responses following an initial relapse in roughly 50% of patients with chemo-sensitive relapse. Patients included were both pediatric and adult with pathologically confirmed HL who have relapsed, refractory, or progressive disease after at least one line of treatment. Demographic and clinical data was collected along with details of treatment and responses to the treatment was observed. Safety assessments included evaluation of adverse events, routine hematology and serum chemistry tests. Data was analyzed in IBM SPSS Statistics V22.0. Descriptive statistics were performed, and categorical variables were expressed as percentages and continuous variables were expressed as mean. this series of 12 patients supports the potential clinical benefit of brentuximab vedotin as a therapeutic option for patients suffering relapse of HL with primary treatment and SCT, with equal response of <PR and >PR in 50% patients and a PFS of 8 months.

Keywords: Brentuximab, Hodgkins Lymphoma, Stem Cell Transplant

Abbreviations

HL: Hodgkin's Lymphoma
ABVD: Doxorubicin, Bleomycin, Vinblastine, Dacarbazine
BEACOPP: Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisolone
ASCT: Autologous Stem Cell Transplantation
R/R: Relapsed/Refractory
PR: Partial Remission
CR: Complete Remission
CI: Confidence Interval
OS: Overall Survival
PFS: Progression Free Survival
HR: Hazard Ratio
RCTs: Randomized Control Trials

1. Introduction

Hodgkin's Lymphoma (HL) accounts for 30 % of all lymphomas [1]. The primary therapy regimens ABVD or BEACOPP are frequently used for Hodgkin's lymphoma [2,3]. Up to 40% of patients with advanced Hodgkin's Lymphoma (HL) experience a relapse after receiving their first therapy, despite current treatment protocols [4]. Autologous Stem Cell Transplantation (ASCT) can produce long-lasting responses following an initial relapse in roughly 50% of patients with chemo-sensitive relapse [5]. However, patients with chemo-resistant cancer prior to transplant have the worst prognosis and frequently recur post ASCT [6,7]. The treatment approaches to achieve remission before ASCT have evolved over the last few years with the introduction of target immunotherapies such as Brentuximab vedotin [8-14].

Because CD30 is expressed on malignant Hodgkin's Reed Sternberg cells of HL and has limited expression on normal cells, CD30 is an attractive target for anti-HL therapy. The microtubule disrupting substance monomethyl auristatin E is coupled to a chimeric Ab specific for human CD30 in brentuximab vedotin. After binding to CD30- expressing cells, the complex is internalized, and monomethyl auristatin E is released, disrupting the microtubule network and subsequently inducing cell-cycle arrest and apoptosis [15,16]. The efficacy of brentuximab in R/R HL has been shown in phase I, phase II and phase III studies key-note study have shown detailed safety profile of single-agent Brentuximab vedotin (1.8 mg/kg intravenously every 3 weeks) giving objective responses in 75% of patients, with CRs observed in 34% of patients and the estimated 12-month survival was 89% and the median Progression-Free Survival (PFS) was 5.6 months [17-19]. Combinations of Brentuximab vedotin with nivolumab have shown good response [20]. Brentuximab vedotin has also been used in combination with Bendamustine with median PFS of 21 months [21]. In this manuscript we are reporting the outcomes of Brentuximab vedotin with Bendamustine in 12 patients who received Brentuximab vedotin on patient access basis.

2. Methodology

Patients included were both pediatric and adult with pathologically confirmed HL who have relapsed, refractory, or progressive disease after at least one line of treatment. The drug was procured through compassionate care program access (via Clinigen). Demographic and clinical data was collected along with details of treatment and responses to the treatment was observed. Safety assessments included evaluation of adverse events, routine hematology and serum chemistry tests. Disease assessments were conducted by the investigator based on the Revised Response Criteria for Malignant Lymphoma according to the institutional standard of care [21]. Patients were categorized as per disease progression as less than PR (Partial Remission) and more than PR for determining efficacy.

Patients receiving various Brentuximab Vedotin containing regimens were compared and their response based on prior received regimens was compared in individual patients.

2.1. Statistical Analysis

Data was analyzed in IBM SPSS Statistics V22.0. Descriptive statistics was performed and categorical variables were expressed as percentages and continuous variables were expressed as mean. Efficacy of brentuximab regimens with respect to disease response (<PR, >PR, Death). Survival analysis was done using cox regression model. All p values were two-sided and a Confidence Interval (CI) of 95% was considered.

3. Results

Patient demographics and disease characteristics are summarized in Table 1. The patients had a mean age of 35.3 years, with males being the predominant patient population (66.66%). None of the patients received up-front brentuximab therapy or a prior transplant. 40% of patients received more than one prior regimen. More than half of the patients (83.33%) had relapsed disease after prior primary regimens, whereas 16.66% were refractory to primary treatment. Most of the patients (75 %) had stage IV disease, whereas others had stage IIA or stage IIIB disease.

Patients were treated with either single-agent brentuximab (25%) or brentuximab with bendamustine regimen (58.33%) or brentuximab with nivolumab regimen (16.66%). Majority of the patients received four (33.33%) and the rest received either 2, 3, or 13 cycles. Patients experienced no ADRs. 33.33% of patients experienced death over-time after brentuximab therapy. Equal numbers of patients had <PR and >PR response (50%). 33.33% and 16.66% of patients had greater >PR response with Brentuximab plus Bendamustine and Brentuximab plus Nivolumab combination respectively. Only two patients underwent autologous stem cell transplant after receiving brentuximab vedotin -containing regimen.

Table 2 shows patient treatment characteristics. Figure 1A and Figure 1B shows the number of patients that responded to Brentuximab vedotin containing regimens and number of prior regimens received respectively Figure 2A and Figure 2B demonstrates the survival curves of patients with relapse/ refractory disease and disease progression after receiving Brentuximab vedotin treatment. The median Overall Survival (OS) time for those who received Brentuximab vedotin containing regimen in relapsed group patients was 59 months. The median Overall Survival (OS) time for patients with <PR disease status was 3 months. Overall Survival rate for patients with relapse disease and <PR disease status was 70% and 50% respectively. The median progression free survival (PFS) was 8 months. The patients with relapsed disease and were found to have better survival probability (HR=27.14; CI= 0.00-10033894.2) which was not statistically significant.

Patient Characteristics	**N = 12 (%)**
Age (Mean)	35.3 years
Male Sex (%)	8 (66.66%)
ECOG Performance Status 0 1	 7 (58.33%) 5 (41.66%)
Time from diagnosis of HL till first dose of Brentuximab vedotin	30 (7 to 40) months

Time from last chemo to Brentuximab vedotin	9 (4 to 12) months
Number of Prior Regimens 1 2 3	 5 (41.66%) 4 (33.33%) 3 (25%)
Disease Status After Last Relapse Relapse Refractory	 10 (83.33%) 2 (16.66%)
Disease Stage Before Starting to Brentuximab Vedotin Stage IIA Stage IV Stage IIIB	 2 (16.66%) 9 (75%) 1 (8.33%)

Table 1: Baseline Patient Characteristics Prior to the First Dose of Brentuximab Vedotin

Characteristic	N= 12 (%)
Regimen Brentuximab (Single-Agent) Brentuximab plus Bendamustine Brentuximab plus Nivolumab	 3 (25%) 7 (58.33%) 2 (16.66%)
Number of Cycles Thirteen Six Four Three Two	 1 (8.33%) 3 (25%) 4 (33.33%) 1 (8.33%) 3 (25%)
Response < PR >PR	 6 (50%) 6 (50%)
Death	4 (33.33%)

Table 2: Details of Brentuximab Vedotin Based Regimens and their Outcomes

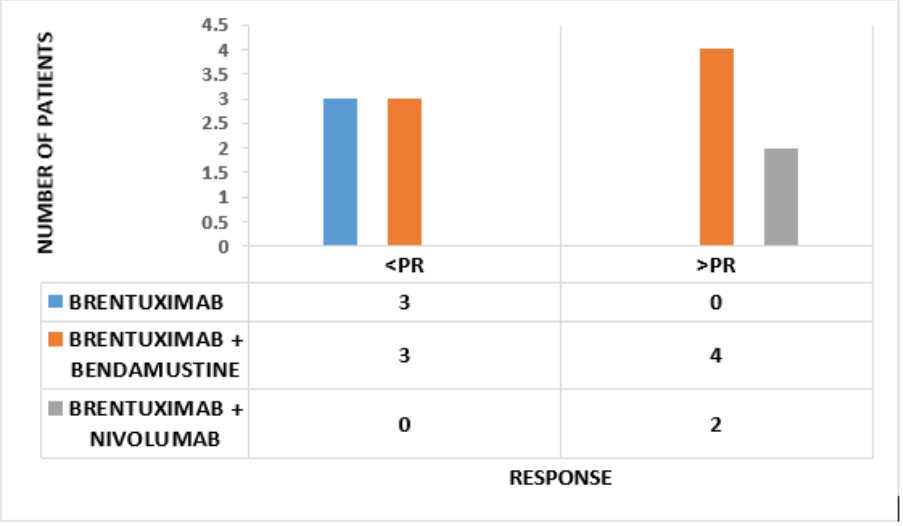

Figure 1A: Number of Patients and Their Response to Brentuximab Vedotin Containing Regimens

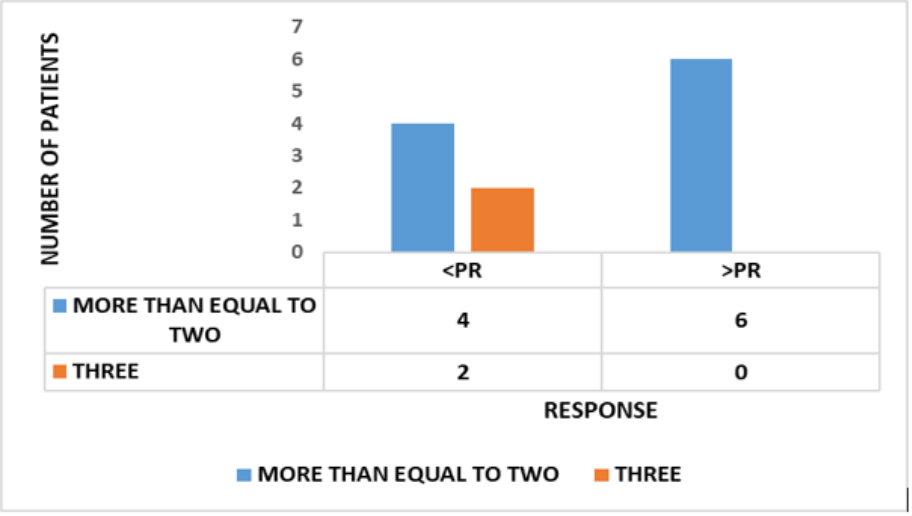

Figure 1B: Number of Patients and their Response to Brentuximab Vedotin Containing Regimens with Respect to Number of Prior Regimens Received

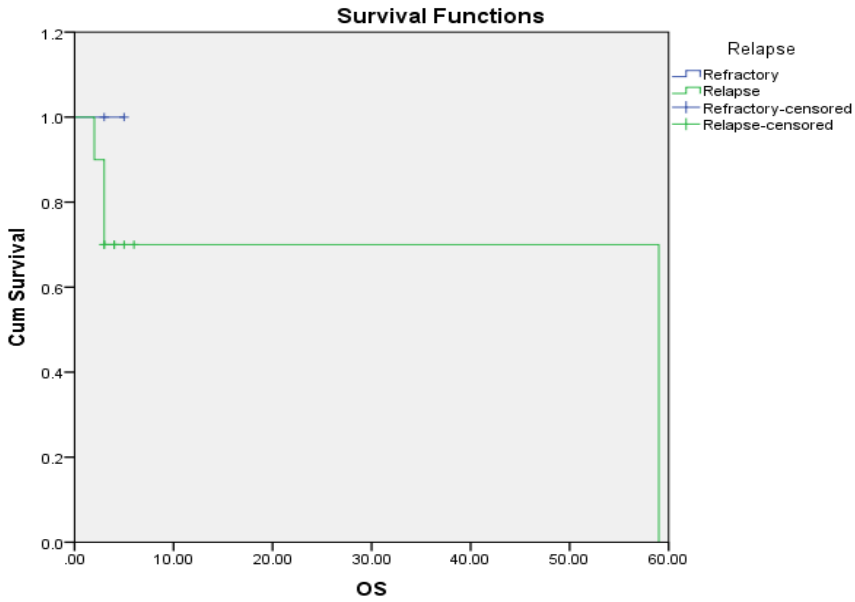

Figure 2A: Kaplan-Meier Curve for Overall Survival (OS) in Patients who Received Brentuximab Vedotin in Relapsed Hodgkin's Lymphoma

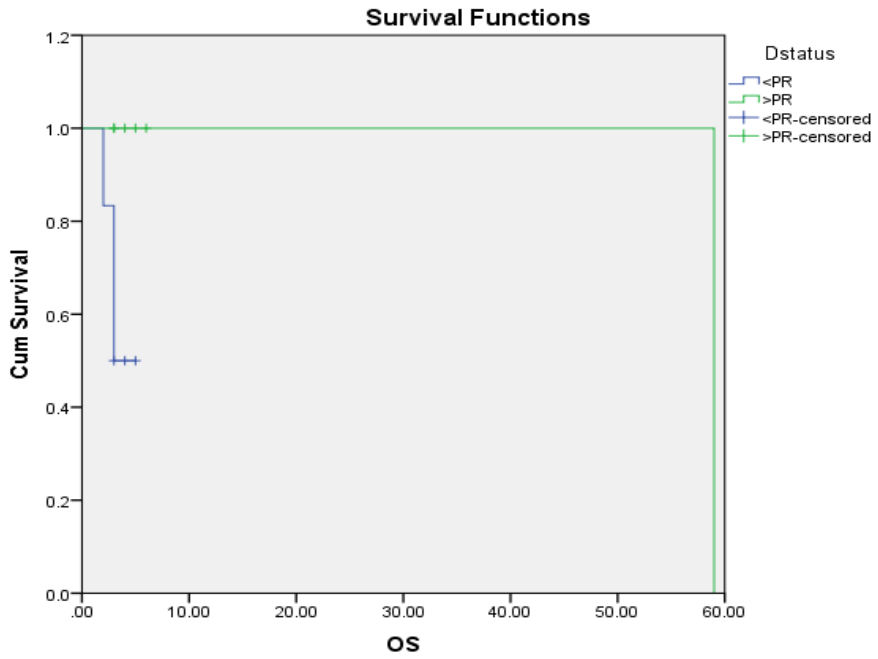

Figure 2B: Kaplan- Meier Curve for Overall Survival (OS) in patients who Received Brentuximab Vedotin Based on Disease Status

Predictor Variables	HR	95%CI	*p-value*
Refractory/Relapse (Relapse)	27.14	(0.00,10033894.2)	0.614
Disease Status (>PR)	0.013	(0.00, 149.37)	0.364

4. Discussion

In the present report, we describe a cohort of 12 patients with HL that relapsed after primary treatment and SCT. Patients were pretreated, with a median of 2 (range, 1-3) treatment regimens before brentuximab vedotin therapy. More than half of the patients under study achieved a response of <PR (57%) and other patients had >PR response (42.8%). Whereas none of the patients achieved a complete remission (CR). The median PFS was 3.9 months and the median OS was not reached, because 4 patients remained alive at the time of data cutoff. On the contrary, Brentuximab vedotin activity in this population contradicted with a pivotal phase 2 trial of 102 patients with HL where patients had CR [17]. This might be due to differences in sample size, variable characteristics of patient population and presence of prior SCT to Brentuximab vedotin therapy. In another two Randomized Control Trials (RCTs) Phase 3 studies, conducted in western population, Brentuximab vedotin showed a good response rate [22-24].

As per Real-world evidence study conducted in India, Brentuximab vedotin plus Bendamustine combination as salvage therapy has shown promising results in middle-income countries (75% Overall Survival Rate) [25]. However, this study showed results for only one type of regimen.

This is the first Indian study demonstrating the response of Brentuximab vedotin as monotherapy versus in other combination regimens of Brentuximab vedotin.

4.1. Limitations

Low sample size could have been a detrimental factor to assess response rate of brentuximab and factors affecting this response. There is a further need to evaluate efficacy and assess factors affecting this response.

5. Conclusion

Despite the selection criteria, this series of 12 patients supports the potential clinical benefit of Brentuximab vedotin as a therapeutic option for patients suffering relapse of HL with primary treatment and SCT, with response of <PR and >PR in 57% and 42.85% patients respectively and a PFS of 3.9 months. Brentuximab vedotin also exhibited a good safety profile. Future studies are required to evaluate the safety and efficacy of Brentuximab vedotin as prophylaxis in the setting of patients at highest risk for disease recurrence.

Authors' Contributions

All authors have equal role in conducting this study.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

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