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Long-term survival outcomes of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: The short-term benefits of brentuximab vedotin (BV) for classical Hodgkin lymphoma (cHL) are well established, but its long-term benefits for refractory/relapsing (r/r) cHL are unknown. A meta-analysis was undertaken to examine the overall survival (OS), and progression-free survival (PFS) from relevant studies with patients with r/r cHL post-autologous stem cell transplantation (ASCT) exposed to BV.

MATERIALS AND METHODS: PubMed, Embase, and the Cochrane library were searched for available papers published up to January 2020. The main outcomes included 3-year OS/PFS and/or 5-year OS/PFS. Data were pooled using random-effects models.

RESULTS: Four studies were included: one randomized controlled trial, one single-arm trial, and two retrospective studies. The four studies included a total of 383 patients (mean of 95.75/study). The proportion of females was 21%-89%. The median age was 26-33 years. The 3-year OS was available for one study and was 41% in patients with r/r cHL with BV after ASCT (OR=0.41, 95% CI: 0.16-0.67). The 5-year OS was available for two studies and was 34% in patients with r/r cHL with BV after ASCT (OR=0.34, 95% CI: 0.19-0.48; mixed-effects model). The 5-year PFS was available for three studies and was 31% in patients with r/r cHL with BV after ASCT (OR=0.31, 95% CI: 0.02-0.61; mixed-effects model).

CONCLUSIONS: The 5-year OS in patients with r/r cHL treated with BV after ASCT is 34% (95 CI: 19%-48%). The 5-year PFS in patients with r/r cHL treated with BV after ASCT is 31% (95 CI: 2%-61%).

Key Words:

Brentuximab vedotin, Hodgkin lymphoma, Autologous stem cell transplantation, Survival, Meta-analysis.

Introduction

Classical Hodgkin's lymphoma (cHL) is a chemotherapy-sensitive disease originating in the lymphatic system and with favorable outcomes[1-3]. The global age-standardized incidence rates are 1.2 per 100,000 men and 0.8 per 100,000 women[4]. About ≥80% of cHL in patients <60 years of age are curable[5]. The management of cHL includes chemotherapy, radiation therapy, and autologous stem cell transplantation (ASCT)[6-8]. The 5-year survival rate of cHL is 86.6% for all stages, 92.3% for localized disease, and 78.2% for distant-stage disease[9].

Despite the high cure rate, the prognosis for many patients who relapse after ASCT is poor, especially for chemorefractory disease[10]. The standard treatment for patients with cHL who are unresponsive to upfront therapy or relapse after primary treatment consists of salvage chemotherapy, followed by high-dose chemotherapy and ASCT[6,7,11,12]. Although this approach achieves long-term progression-free survival (PFS) in 50-60% of patients with chemosensitive relapse, outcomes remain poor in primary chemorefractory disease[12,13]. The long-term survival of patients with relapsed/refractory Hodgkin lymphoma (r/r HL) and chemoresistant disease rarely exceeds 15%-17%, with a median survival of 24 months[14,15]. Therefore, determining novel treatment strategies that optimize the outcomes of high-dose regimens and auto-SCT remains a priority for r/r cHL patients[12].

Brentuximab vedotin (BV) is an anti-CD30 monoclonal antibody conjugated to the microtubule-disrupting agent monomethyl-auristatin E and has shown significant clinical efficacy in cHL[12,16]. BV potentially induces deep responses when applied in the context of a first salvage treatment before ASCT, even as a single agent[17]. BV can rapidly induce positron emission tomography (PET) negativity without severe toxicity, which represents a major advance in patient

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management, allowing the timely application of ASCT[12,17]. BV's high efficacy and low toxicity profile resulted in a plethora of clinical trials investigating its role either as monotherapy or in combination with chemotherapy and/or newer agents in different treatment phases [including first-line treatment and even after allogeneic SCT (allo-SCT) failure][18-20], as well as in other malignancies[21]. Specifically, regarding r/r cHL, BV has been approved as first-line therapy by the Food and Drug Administration (FDA) in 2017.

Even though many narrative reviews and randomized control trials (RCTs) have speculated the benefit of BV regarding short-term survival outcomes, the available evidence for long-term benefits in overall survival (OS) and PFS is the relative effectiveness of BV in comparison with other treatment modalities[12,16,17,22-24]. A systematic review examined the absolute long-term survival outcome after treatment with BV, but it only included two studies, and one needed to be updated[25]. Therefore, due to the extremely small amounts of published results on the long-term outcomes of BV, a meta-analysis was undertaken to identify the OS and PFS from relevant studies with patients with r/r cHL post-ASCT exposed to BV.

Materials and Methods

Literature Search

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[26]. We started by searching for relevant articles using the PICO principle[27]. The eligibility criteria were 1) population: patients who received a diagnosis of r/r cHL following ASCT, 2) interventions: BV as single agent or a salvage chemotherapy regimen, 3) outcome: the study reported 3- or 5-year OS/PFS alone with its 95% CI, and HR, if available, and 4) in English. PubMed, Embase, and the Cochrane library were searched for available papers published up to January 2020, using the MeSH term 'Hodgkin Disease', as well as relevant keywords.

Data Extraction

Two authors extracted study characteristics (authors, year of publication, country, disease type, sample size, female percentage, and mean age), treatment parameters (before BV, dose of BV, median cycles of BV, and median follow-up), the main outcome (3-year OS, 3-year PFS, 5-year OS, and/or 5-year PFS), and secondary outcome (reported median OS and reported median PFS). Discrepancies were solved by discussion.

Quality of the Evidence

No restrictions were set regarding the study type due to the limited number of RCTs and observational studies in this field. Four studies entered the meta-analysis (one RCT, one single-arm trial, and two retrospective studies). The two retrospective cohort studies[22,24] did not include a comparison group; hence we modified the total score of the Newcastle-Ottawa Scale (NOS) criteria[28] from nine to six criteria (the criteria that assess the comparison group were excluded). The RCT was assessed using the Cochrane criteria[29]. The single-arm trial was evaluated by the Methodological index for non-randomized studies (MINORS: 8-point scale)[30]. The level of evidence of all articles was assessed independently by two authors. Discrepancies in the assessment were solved through discussion until a consensus was reached.

Statistical Analysis

All analyses were performed using STATA SE 14.0 software (StataCorp, College Station, TX, USA). The effects and corresponding 95% confidence intervals (CIs) were used to compare the outcomes. Statistical heterogeneity among the studies was calculated using Cochran's Q-test and the I^2 index. I^2 >50% and p<0.10 in the Q-test indicated high heterogeneity, and the random-effects model was used; otherwise, the fixed-effects model was applied. Because we only extracted the outcome parameters in the BV group, there was no p-value for group differences. Potential publication bias by funnel plots and Egger's test were performed.

Results

Selection of the Studies

Figure 1 presents the study selection process. A total of 234 records were first retrieved. After removing 80 duplicates, 154 records were screened, 13 were excluded, and 141 full-text papers were assessed for eligibility. A total of 137 papers were excluded: three for publication type, 11 for study aims, eight for the study population, 58

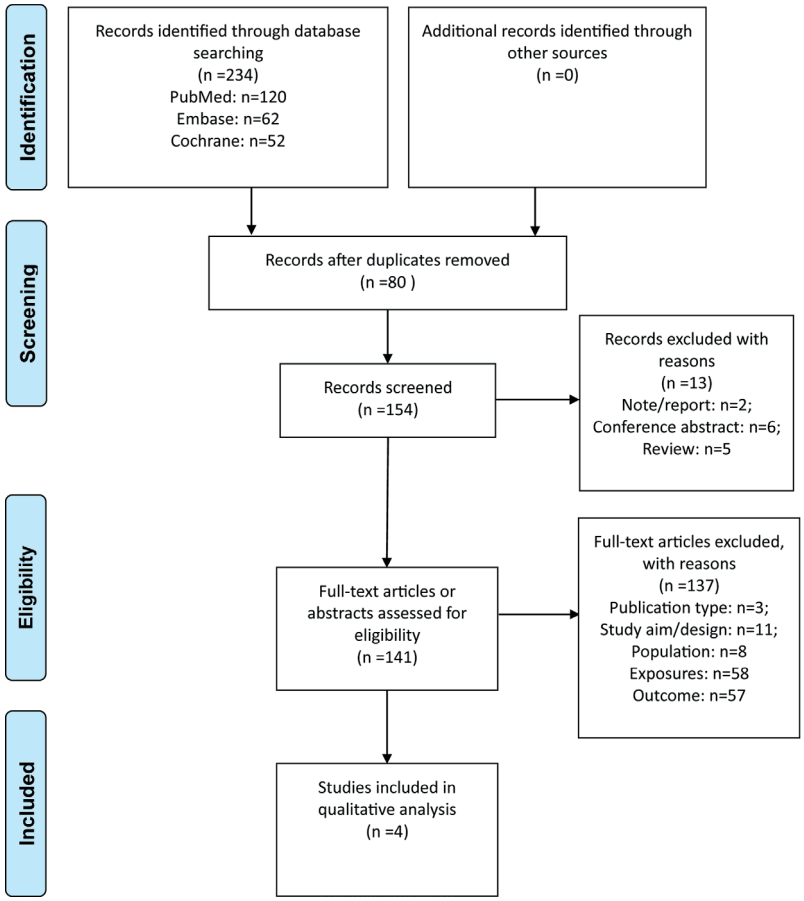

Figure 1. Flow diagram.

for exposures, and 57 for outcomes. Finally, four studies were included: one RCT[31], one single-arm trial[23], and two retrospective studies[22,24] (Table I). The four studies included a total of 383 patients (mean of 95.75/study). The proportion of females was 21%-89%. The median age was 26-33 years. The RCT[31] had a high risk of bias for allocation concealment (**Supplementary Table I**). The two retrospective studies scored 6 points each[22,24] (**Supplementary Table II**). The single-arm trial scored 7/8 points[23] (**Supplementary Table III**).

Overall Survival

The 3-year OS was available for one study[24] and was 41% in patients with r/r cHL with BV after ASCT (OR=0.41, 95% CI: 0.16-0.67). The 5-year OS was available for two studies[22,23] and was 34% in patients with r/r cHL with BV after ASCT (OR=0.34, 95%CI: 0.19-0.48). Heterogeneity was observed (I^2=74.4%, p=0.048), and the mixed-effects model was used (Figure 2A and Table II). The sensitivity analysis suggested that none of the studies affected the results of the OS meta-analysis (**Supplementary Figure 1**).

Progression-Free Survival

The 5-year PFS was available for three studies[22,23,31] and was 31% in patients with r/r cHL with BV after ASCT (OR=0.31, 95% CI: 0.02-0.61). Heterogeneity was observed (I^2=97.3%, p<0.001), and the mixed-effects model was used (Figure 2B and Table II). The sensitivity analysis suggested that the study by Moskowitz et al[31] affected the results of the PFS meta-analysis (**Supplementary Figure 2**).

Publication Bias

There were no publication biases among the studies regarding OS (**Supplementary Figure 3**), but a publication bias was observed for PFS according to the funnel plot (**Supplementary Figure 4**). On the other hand, Begg's and Egger's tests indicated no publication bias (Table III).

Discussion

The short-term benefits of BV for cHL are well established, but its long-term benefits for r/r cHL

Table I. Literature search and study characteristic.

Author, Year	Country	Study design	Pre-treatment with BV	Dose of treatment	Median cycles of BV	Median follow-up, months	Reported median OS, 95% CI	Reported median PFS, 95% CI	No. of patients treated with BV	Female, %	Mean age (SD)
Moskowitz et al, 2018[31]	USA	RCT	Prior treatment of auto-SCT,	1.8 mg/kg per 3 weeks for maximum of 16 cycles	15 (1-16)	30 (0-50)	NR	42.9 (30.4-42.9)	165	89	33 (18-71)
Chen et al, 2016[23]	USA	Single-arm	History of chemotherapy and auto-SCT, no history of allo-SCT	1.8 mg/kg per 3 weeks for maximum of 16 cycles	NR	35.1 (1.8-72.9)	40.5 (28.7, 61.9)	9.3 (7.1,12.2)	102	54	31 (15-77)
Kral et al, 201924	Czech Republic	Retrospective	Received a median of 3 treatment regimens before BV (ABVD, BEACOPP, DHAP, ICE)	1.8 mg/kg per 3 weeks for maximum of 16 cycles	7.5 (3-16)	4.3 (1.2-16.0) years	NR	1.38 (0.58-2.21) years	58	25	30.5 (20.0-53.0)
Ozbalak et al, 2019[22]	Turkey	Retrospective	Received at least 2 courses of BV	1.8 mg/kg per 3 weeks for up to 18 cycles	7 (2-18)	20 (4-84)	18.5	6	58	21	26 (13-62)

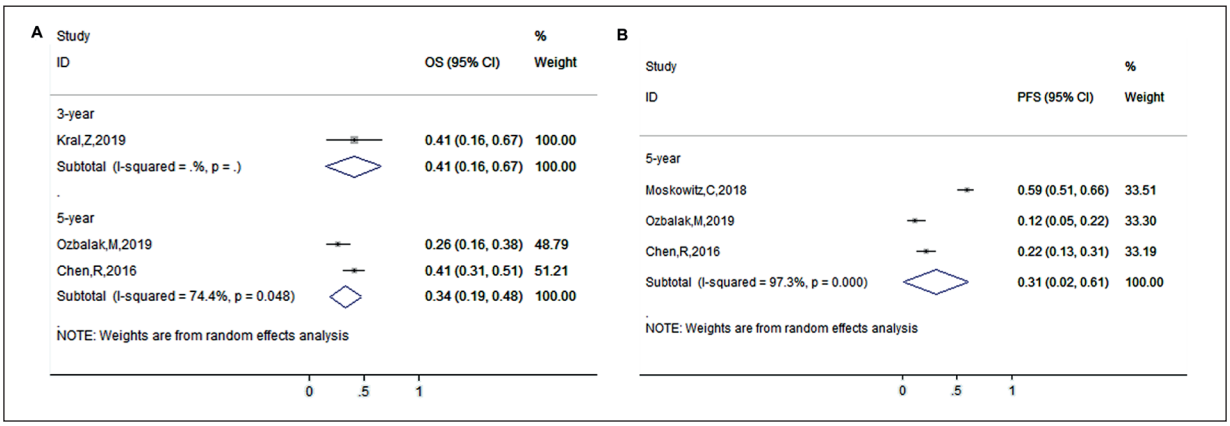

Figure 2. A, OS. **B,** PFS.

Table II. OS and PFS.

	N	ES (95% CI)	I-square	*p* (Heterogeneity)
OS				
3-year	1	0.41 (0.16, 0.66)	.	
5-year	2	0.34 (0.19, 0.48)	74.4%	0.048
PFS				
5-year	3	0.31 (0.02, 0.60)	97.3%	< 0.001

are unknown. Therefore, this meta-analysis was undertaken to examine the OS and PFS from relevant studies with patients with r/r cHL post-ASCT exposed to BV. The results indicated that the 5-year OS in patients with r/r cHL treated with BV after ASCT was 34% (95 CI: 19%-48%). The 5-year PFS in patients with r/r cHL treated with BV after ASCT was 31% (95 CI: 2%-61%). So far, this meta-analysis is the largest one quantifying the absolute benefit of BV in patients with r/r cHL after ASCT.

The present study showed that the 5-year OS of patients with r/r cHL who received BV after ASCT was 34% and that the 5-year PFS was 31%. This survival is better than the long-term survival observed in patients with r/r HL and chemoresistant disease (15%-17%), with a median survival of 24 months[14,15]. The results observed here might be comparable with other therapies, but the comparisons are difficult because of the variety of reported outcomes. The CheckMate 205 trial showed that nivolumab led to a median PFS of 14.7 months and a 2-year OS of 87%[32]. Another limitation of the present study is that the response status to chemotherapy before ASCT could not be considered in the present study. Indeed, a study revealed that the 5-year PFS of patients who received high-dose chemotherapy for r/r cHL was 69.4%, 54.2%, and 18.5% in those who achieved a complete response, partial response, or less than partial response before ASCT[33]. Furthermore, a previous meta-analysis[34] showed that BV had better survival in patients with r/r cHL after failure to ASCT than other therapies, such as bendamustine, donor leukocyte infusion, allo-SCT, bortezomib, lenalidomide, perifosine, sorafenib, and panobinostat.

Table III. Publication bias.

	N	Begg's tes		Egger's test	
		Z-score	*p*	T-score	*p*
OS	3	-0.52	0.602	0.13	0.917
PFS	3	-0.52	0.602	-1.87	0.313

A pooled cohort analysis[35] of patients who received BV after ASCT for r/r cHL showed 1-year OS and PFS of 79.5% and 47.6%, respectively. Stranzenbach et al[36] reported good outcomes with 1.8 mg/kg of BV every 3 weeks. A recent systematic review analyzed the long-term survival outcome in patients with r/r cHL treated with BV after failed ASCT, but it only contained two studies, and one needed to be updated[25]. The present meta-analysis included four studies, including the updated one from Kaloyannidis et al[25], and showed a comparable 5-year PFS (32.2% *vs*. 31%) but a higher OS (92.2% *vs*. 34%). Of course, the included studies play an important part in meta-analyses, probably explaining this important difference. In addition, the 5-year survival reported here was similar to that reported in the pivotal study of BV[23], included in this meta-analysis. The 5-year PFS HR reported by Moskowitz et al[31] showed a significant protective effect of BV in patients with r/r cHL compared to those treated with placebo, indicating the effective long-term survival outcome of BV. Nevertheless, Bazarbachi et al[15] found that pre-allograft BV had no significant effect on PFS or OS among patients with cHL over a long-term period (3-year PFS HR: 1.16, 95% CI: 0.87-1.55). It might indicate that BV treatment can yield better outcomes among patients with advanced HL stages compared to cHL. Nevertheless, this will have to be examined in future studies.

The results of the present meta-analysis must be considered along with its limitations. The included studies may bias the outcomes of interest since they were conducted at various institutions. The baseline characteristics of the patients from different studies and the involved physicians may bias the results. Because of the small number of studies, we could include only four studies, and their type was different. Some studies fell short in terms of quality, due to small numbers of participants, unclear reporting of study methods, and data reporting in a format that was not easy to combine with other data. Potential publication bias by funnel plots and Egger's test were performed, but the results have to be taken with caution because the number of studies included in the meta-analysis was less than ten, in which case the funnel plots and Egger's test could yield misleading results[37]. Further research is required to clarify the long-term effectiveness and safety of BV treatment for r/r cHL patients. Since BV is a well-tolerated antibody conjugate drug and is considered a standard treatment for patients with r/r cHL, studies that include no BV in the control group might lead to ethical issues. Hence, our results only presented the long-term survival outcomes.

Conclusions

As a result of our investigation, the 5-year OS of BV in patients with r/r cHL is 34% (95 CI: 19%-48%). The 5-year PFS of BV in patients with r/r cHL is 31% (95 CI: 2%-61%). Large-sample RCTs should be conducted to investigate the long-term survival outcome of r/r cHL patients and determine the best treatment options. Long-term studies of BV in comparison with other therapies in r/r cHL treatment should be performed.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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