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 outcomes1-3. The global age-standardized incidence rates are 1.2 per 100,000 men and 0.8 per 100,000 women4. About ≥80% of cHL in patients <60 years of age are curable5. 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 disease9.

Despite the high cure rate, the prognosis for many patients who relapse after ASCT is poor, especially for chemorefractory disease10. 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 ASCT9,11,12. Although this approach achieves long-term progression-free survival (PFS) in 50-60% of patients with chemosensitive relapse, outcomes remain poor in primary chemorefractory disease12,13. 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 months14,15. Therefore, determining novel treatment strategies that optimize the outcomes of high-dose regimens and auto-SCT remains a priority for r/r cHL patients12.

Brentuximab vedotin (BV) is an anti-CD30 monoclonal antibody conjugated to the microtubule-disrupting agent monomethyl-austatin E and has shown significant clinical efficacy in cHL12,16. BV potentially induces deep responses when applied in the context of a first salvage treatment before ASCT, even as a single agent17. BV can rapidly induce positron emission tomography (PET) negativity without severe toxicity, which represents a major advance in patient
管理，允许及时应用ASCT。BV的高疗效和低毒性特征导致了对其在不同治疗阶段（包括一线治疗和/或细胞基因组学SCT（allo-SCT）失效）以及其他恶性肿瘤中的大量临床试验的研究，包括非霍奇金淋巴瘤（r/r cHL）。尤其是关于r/r cHL，BV已被FDA批准作为2017年的一线治疗。

尽管许多叙述性评论和随机对照试验（RCTs）推测了BV在短期生存结果中的益处，但现有的证据关于OS和PFS的长期益处与各种治疗方案相对有效性的比较仍然有限。12,16,17,22-24。一项系统性回顾研究评估了治疗后BV的绝对长期生存结果，但只包括了两篇文献，其中一篇需要更新。因此，由于长期结果的文献非常少，因此进行了一项元分析，以确定与ASCT后暴露于BV的r/r cHL患者相关的OS和PFS。

### 材料和方法

#### 文献检索

这项元分析根据 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 指南进行。我们按照PICO原则开始检索相关文献。1) 人口：接受ASCT后再诊断为r/r cHL的患者，2) 干预：单药BV或挽救化疗方案，3) 结果：报告的3年OS/3年PFS、5年OS/5年PFS，以及2) 4) 在英语中。PubMed、Embase和Cochrane图书馆被用于检索到2020年1月的文献，使用MeSH术语‘Hodgkin Disease’，以及相关的关键词。

#### 数据提取

两位作者提取了研究特征（作者、发表年份、国家、疾病类型、样本大小、女性比例、均年龄）、治疗参数（在BV作用下、剂量和周期数）和相关结果（报告的OS和PFS）。

#### 质量评价

不设定任何关于研究类型的限制，因为我们只检索了四篇研究（一篇RCT、一篇单臂试验和两篇回顾性研究）。两篇回顾性队列研究22,24没有设置比较组，因此我们需要对Newcastle-Ottawa Scale (NOS) 标准评估的九个标准中的一部分进行修正，其中比较组的评估标准被移除。RCT和单臂试验分别评估了Cochrane标准和Methodological Index for Non-Randomized Studies (MINORS: 8-point scale)30。所有文献的水平评价由两名作者独立进行。如果存在分歧，则通过讨论至达成共识。

#### 统计分析

所有分析使用STATA SE 14.0软件（StataCorp，College Station，TX，USA）进行。统计了各结果的95%置信区间（CIs）和p值。统计了各结果的95%置信区间（CIs）和p值。由于我们只提取了BV组的结果，因此没有组间差异的p值。通过Funnel plots和Egger’s test进行了潜在的发表偏倚的评估。
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.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Study design</th>
<th>Pre-treatment with BV</th>
<th>Dose of treatment</th>
<th>Median cycles of BV</th>
<th>Median follow-up, months</th>
<th>Reported median OS, 95% CI</th>
<th>Reported median PFS, 95% CI</th>
<th>No. of patients treated with BV</th>
<th>Female, %</th>
<th>Mean age (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moskowitz et al, 2018³¹</td>
<td>USA</td>
<td>RCT</td>
<td>Prior treatment of auto-SCT, for maximum of 16 cycles</td>
<td>1.8 mg/kg per 3 weeks</td>
<td>15 (1-16)</td>
<td>30 (0-50)</td>
<td>NR</td>
<td>42.9 (30.4-42.9)</td>
<td>165</td>
<td>89</td>
<td>33 (18-71)</td>
</tr>
<tr>
<td>Chen et al, 2016³³</td>
<td>USA</td>
<td>Single-arm</td>
<td>History of chemotherapy and auto-SCT, no history of allo-SCT</td>
<td>1.8 mg/kg per 3 weeks for maximum of 16 cycles</td>
<td>NR</td>
<td>35.1 (1.8-72.9)</td>
<td>40.5 (28.7, 61.9)</td>
<td>9.3 (7.1,12.2)</td>
<td>102</td>
<td>54</td>
<td>31 (15-77)</td>
</tr>
<tr>
<td>Kral et al, 2019²⁴</td>
<td>Czech Republic</td>
<td>Retrospective</td>
<td>Received a median of 3 treatment regimens before BV (ABVD, BEACOPP, DHAP, ICE)</td>
<td>1.8 mg/kg per 3 weeks for maximum of 16 cycles</td>
<td>7.5 (3-16)</td>
<td>4.3 (1.2-16.0) years</td>
<td>NR</td>
<td>1.38 (0.58-2.21) years</td>
<td>58</td>
<td>25</td>
<td>30.5 (20.0-53.0)</td>
</tr>
<tr>
<td>Ozbalak et al, 2019²²</td>
<td>Turkey</td>
<td>Retrospective</td>
<td>Received at least 2 courses of BV</td>
<td>1.8 mg/kg per 3 weeks for up to 18 cycles</td>
<td>7 (2-18)</td>
<td>20 (4-84)</td>
<td>18.5</td>
<td>6</td>
<td>58</td>
<td>21</td>
<td>26 (13-62)</td>
</tr>
</tbody>
</table>
Brentuximab vedotin for r/r cHL: a meta-analysis

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\cite{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\%\cite{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\cite{33}. Furthermore, a previous meta-analysis\cite{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, bortezomb, lenalidomide, perifosine, sorafenib, and panobinostat.

Table II. OS and PFS.

<table>
<thead>
<tr>
<th>N</th>
<th>ES (95% CI)</th>
<th>I-square</th>
<th>p (Heterogeneity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>3-year 1</td>
<td>0.41 (0.16, 0.66)</td>
<td>74.4%</td>
</tr>
<tr>
<td></td>
<td>5-year 2</td>
<td>0.34 (0.19, 0.48)</td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>5-year 3</td>
<td>0.31 (0.02, 0.60)</td>
<td>97.3%</td>
</tr>
</tbody>
</table>

Table III. Publication bias.

<table>
<thead>
<tr>
<th>N</th>
<th>Begg's tes</th>
<th>Egger's test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Z-score</td>
<td>p</td>
</tr>
<tr>
<td>OS</td>
<td>-0.52</td>
<td>0.602</td>
</tr>
<tr>
<td>PFS</td>
<td>-0.52</td>
<td>0.602</td>
</tr>
</tbody>
</table>
A pooled cohort analysis\(^\text{15}\) 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\(^\text{36}\) 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\(^\text{25}\). The present meta-analysis included four studies, including the updated one from Kaloyannidis et al\(^\text{25}\), 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\(^\text{25}\), included in this meta-analysis. The 5-year PFS HR reported by Moskowitz et al\(^\text{31}\) 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\(^\text{15}\) 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\(^\text{37}\). 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.

**Funding**

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