

Brentuximab vedotin for treatment of relapsed or refractory malignant lymphoma: results of a systematic review and meta-analysis of prospective studies

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Background: Recently, brentuximab vedotin has become a promising therapeutic approach for CD30-positive hematological malignancies, but its role in other relapsed or refractory malignant lymphoma needs to be proven. Brentuximab vedotin was demonstrated effective, but no study has summarized the concrete effect of brentuximab vedotin in malignant lymphoma. To truly know the role of brentuximab vedotin, we performed a systematic review of the literature and a meta-analysis of all known prospective trials, to assess the value of brentuximab vedotin for patients with relapsed and refractory malignant lymphoma.

Methods and materials: This was a systematic review of publications indexed in the PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and ISI Web of Knowledge performed on February 10, 2015. Six studies, including 302 patients were identified. Meta-analyses were carried out to calculate the objective response rate (ORR), complete response rate (CRR), and partial response rate (PRR) of brentuximab vedotin for malignant lymphoma.

Results: In patients with malignant lymphoma, ORR was 0.61, CRR was 0.38, and PRR was 0.51. High heterogeneity between studies was observed, and funnel plots were not symmetrical, which means that publication bias existed. Brentuximab vedotin was generally well-tolerated by patients reported in the included studies; adverse effects also occurred, but they were considered manageable.

Conclusion: Our analysis revealed a promising benefit of brentuximab vedotin in the treatment of relapsed and refractory malignant lymphoma. Larger sample of randomized controlled clinical trials are needed in the future.

Keywords: clinical studies, monoantibody, lymphoma, clinical studies

Introduction

Malignant lymphoma is one of the most common cancers among people all over the world.¹ Due to the development of highly active chemotherapy and the optimization of radiotherapy in recent years, patients with newly diagnosed lymphoma have a very excellent prognosis, and their 5-year progression-free survival rate can be as high as greater than 75%.² Curing patients whose disease are relapsed after transplantation or refractory after salvage chemotherapy remains a big clinical challenge; such patients are rarely cured and only have a median overall survival of 2–3 years.^{2–5}

Brentuximab vedotin (SGN-35) is a CD30-directed antibody-drug conjugate (ADC), which can induce cell-cycle arrest and apoptosis, with proven efficacy in patients with CD30-positive malignancies, including Hodgkin lymphoma (HL), peripheral T-cell lymphoma, diffuse large B-cell lymphoma, and systemic anaplastic

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large-cell lymphoma (SALCL).⁶ Because of its significant clinical efficacy, brentuximab vedotin was approved by the US Food and Drug Administration (FDA) in 2011 for patients with classical HL or SALCL who have relapsed disease after autologous hematopoietic stem cell transplantation or who have progressive disease after at least two lines of multiagent chemotherapy and are not suitable candidates for autologous hematopoietic stem cell transplantation.^{7–10} However, its role in other relapsed or refractory malignant lymphoma needs to be proven. Various clinical trials^{3,10,13–18} have demonstrated brentuximab vedotin has efficacy and safety, with acceptable toxicity; however, no study has summarized the concrete effect of brentuximab vedotin in malignant lymphoma. Therefore, in order to truly know whether the brentuximab vedotin is effective in the treatment of malignant lymphoma, we performed a systematic review of the literature and a meta-analysis of all known prospective trials, to assess the value of brentuximab vedotin for patients with relapsed and refractory malignant lymphoma.

Materials and methods

Search strategy

A systematic review of publications indexed in PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and ISI Web of Knowledge were performed on February 10, 2015 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.¹¹ The search strategy included the following phrases of “brentuximab vedotin” pairing independently with “lymphoma” or “malignant lymphoma”. The reference lists were screened for all of the identified studies and for the comprehensive reviews in the field.

Inclusion and exclusion criteria

For inclusion, the trials had to be prospective randomized controlled trials (RCTs) or observational trials examining brentuximab vedotin as a treatment for relapsed or refractory lymphoma. We only included full-text publications and did not apply any restriction on age, sex, or ethnicity. Retrospective studies, case reports, and review articles were excluded. When multiple publications reported on the same population, only the most recent study was included.

Data extraction and quality assessment

Two reviewers (RZC and FW) independently selected studies by examining titles and abstracts to determine those potentially relevant to our study question. The reported

results of these identified studies were further analyzed a third one (best alternative care) for inclusion. Disagreement was settled by discussion and review of the articles by all the authors. The following information was extracted for each study: (1) the first author's last name; (2) year of publication; (3) country of study; (4) name of study (if available); (5) study design; (6) number of subjects; (7) mean age of subjects; (8) definition of relapsed or refractory lymphoma; (9) the procedure and duration of treatment of brentuximab vedotin; (10) effect size (relative risk [RR] and 95% confidence interval [CI]); and (11) the adverse effect of brentuximab vedotin. Quality of the included cohort prospective studies was evaluated using the Newcastle–Ottawa scale, modified for assessment of bias.¹²

Statistical analysis

As there were so few published studies examining our area of interest, meta-analyses were not stratified by any types of lymphoma. However, the use of a random-effects model should account for some of the interstudy variation. All statistical analyses were conducted using STATA (version 12.0; StataCorp; College Station, TX, USA) software. We estimated RR with 95% CI using the standardized mean difference. All test results were thought to be statistically significant at $P < 0.05$. Heterogeneity was evaluated by using I^2 values, and significant heterogeneity was considered to be present when the I^2 statistic was $> 50\%$. Potential publication bias was assessed by funnel plots.

Results

Literature search

We initially identified 278 potentially eligible studies, and 156 studies were considered as potential studies. After screening the title or abstract, 136 studies were excluded, as indicated in Figure 1. A total of 20 studies were retrieved and evaluated in detail, and finally, six complete peer-reviewed papers met our selection criteria and were included in this meta-analysis.

Study characteristics and qualities

Table 1 shows the design features and participant characteristics of the studies, which included six single-arm prospective clinical trials.^{13–18} A total of 302 patients were selected in this study, including patients with HL, SALCL, B-cell lymphomas, such as diffuse large B-cell lymphoma, and T-cell lymphomas, such as peripheral T-cell lymphoma. The overall quality of these six studies was high according to the Newcastle–Ottawa scale (Table 2).¹²

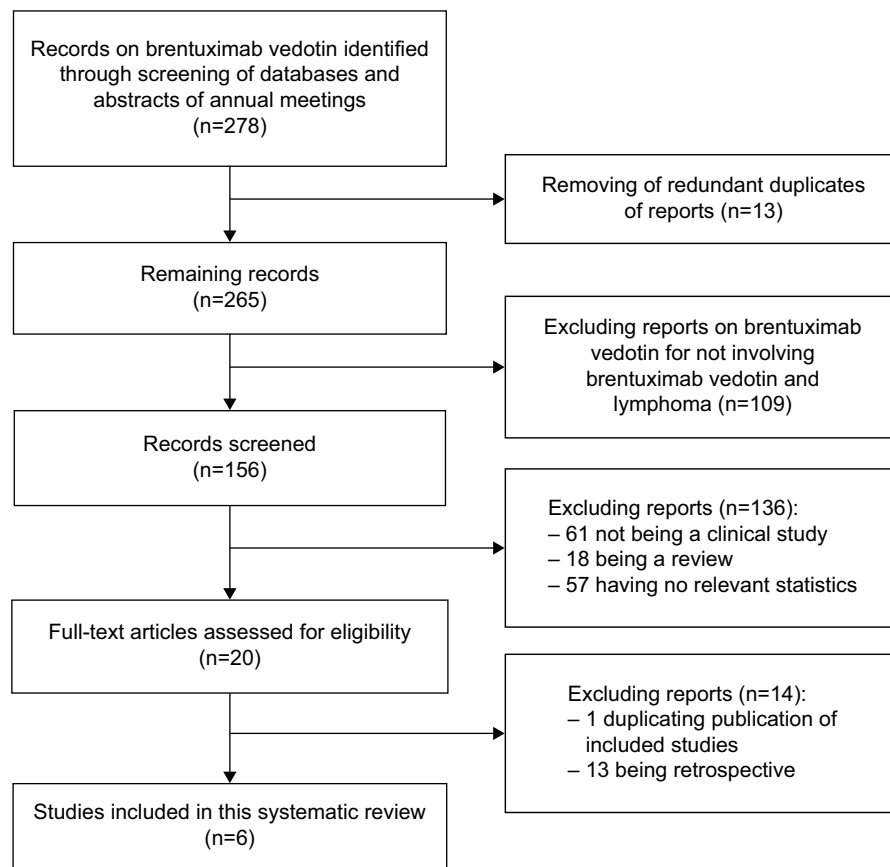


Figure 1 Flow chart. The outcome of the comprehensive search strategy to identify studies meeting selection criteria for the meta-analysis.

Responses of brentuximab vedotin in the treatment of malignant lymphoma

Data on the objective response rate (ORR) (the rate of complete response plus partial response) were extracted from the six studies selected (300 patients).^{13–18} A random-effects model was chosen, and a high heterogeneity between studies ($I^2 = 90.9\%$) was observed. The pooled proportion of ORR was 0.61 (95% CI 0.44 to 0.79, $P < 0.05$) (Figure 2A). The funnel plot was not very symmetrical, which means that publication bias existed (Figure 2B). Data on the complete response rate (CRR) were extracted, and a high heterogeneity also existed ($I^2 = 87.6\%$). The pooled proportion of CRR was 0.38 (95% CI 0.23 to 0.53, $P < 0.05$) (Figure 3A), while the funnel plot was not generally symmetrical, which means that there might have been a publication bias within those studies (Figure 3B). Data on partial response rate (PRR) were extracted, and heterogeneity existed between these six studies ($I^2 = 56.8\%$). The pooled proportion of PRR was 0.25 (95% CI 0.17 to 0.33, $P < 0.05$) (Figure 4A), and the funnel plot was not generally symmetrical, which means that there might have been a publication bias within those studies (Figure 4B).

Adverse effects of brentuximab vedotin

Because of the different kinds of lymphoma, it is very hard to summarize the concrete adverse effect of all the studies. Overall, brentuximab vedotin was generally well-tolerated by patients reported in the included studies;^{13–18} adverse effects also occurred, but most of them were considered manageable. Common adverse effects included neutropenia, thrombocytopenia, diarrhea, hyperglycemia, fatigue, nausea, arthralgia, pyrexia, and peripheral neuropathy. The rate of adverse events of at least grade 3 were above 50% in the studies reported, but only a few patients died because of these adverse effects, and the reason for these deaths included disease progression, infection, or some unknown reasons according to different studies.

Discussion

Main findings

Brentuximab vedotin is a promising agent in the treatment of CD30-positive malignancies; however, no previous studies have summarized its concrete effect in relapsed or refractory lymphoma. In this meta-analysis, we included six clinical trials and summarized the results of ORR, CRR,

Table 1 Characteristics of studies included in this survey

| Study | Number | Median age (range) | Design | Primary disease | Disease characteristics | Dosage and cycle of brentuximab vedotin |
|------------------------------|----------------------------------|---|-------------------------|--------------------------|--|--|
| Gopal et al ¹³ | 25 | 32 (20–56) | Prospective, Phase II | HL | > 100 days after alloSCT, had no active GVHD, and received a median of 9 (range 5–19) prior regimens. | 1.2 (n=6) or 1.8 (n=19) mg/kg every 3 weeks (median 8 cycles; range 1–16). |
| Pro et al ¹⁴ | 58 | 52 (14–76) | Prospective, Phase II | SALCL | Relapsed or refractory SALCL after treatment failure of at least one prior therapy with curative intent. | 1.8 mg/kg intravenously every 3 weeks over 30 minutes. |
| Gopal et al ¹⁵ | 102 | 31 (15–77) | Prospective, Phase II | HL | Relapsed/refractory HL after auto-SCT. | 1.8 mg/kg intravenously once every 3 weeks over 30 minutes on an outpatient basis for up to 16 infusions. |
| Horwitz et al ¹⁶ | 35 | 64 (33–83) | Prospective, Phase II | T-cell lymphomas | Relapsed T-cell lymphomas included PTCLs, specifically AITL and PTCL-NOS. | 1.8 mg/kg was administered every 3 weeks until progression or unacceptable toxicity. |
| Ogura et al ¹⁷ | 14 (HL: 9, SALCL: 5) | HL: 32 (22–88) SALCL: 44 (37–66) | Prospective, Phase I/II | HL, SALCL | Relapsed or refractory CD30-positive HL or SALCL. | 1.8 mg/kg was given to 14 patients (9 with Hodgkin's lymphoma and 5 with SALCL). The median number of treatment cycles was 16 (range 4–16). |
| Jacobsen et al ¹⁸ | 68 (DLBCL: 49, other B-cell: 19) | DLBCL: 62 (17–85) Other B-cell: 36 (16–68) | Prospective, Phase II | DLBCL, other B-cell NHLs | Relapsed/refractory NHLs, including DLBCL and other B-cell NHLs. | Patients received 1.8 mg/kg brentuximab vedotin intravenously every 3 weeks. Those who achieved stable disease or better could receive continued treatment until disease progression, unacceptable toxicity, or study closure. |

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; alloSCT, allogeneic stem cell transplantation; auto-SCT, autologous stem cell transplantation; DLBCL, diffuse large B-cell lymphoma; GVHD, graft-versus-host disease; HL, Hodgkin lymphoma; NHLs, non-Hodgkin lymphomas; PTCL-NOS, peripheral T-cell lymphoma, non otherwise specified; PTCLs, peripheral T-cell lymphomas; SALCL, systemic anaplastic large-cell lymphoma.

Table 2 Quality of included studies

| Study | Representativeness of study sample | Ascertainment of exposure | Demonstration outcome was not present at start | Detection bias minimized | Attribution bias minimized | Follow-up time appropriate |
|------------------------------|------------------------------------|---------------------------|--|--------------------------|----------------------------|----------------------------|
| Gopal et al ¹³ | Yes | Yes | Yes | Yes | Yes | Yes |
| Pro et al ¹⁴ | Yes | Yes | Yes | Yes | Yes | Yes |
| Gopal et al ¹⁵ | Yes | Yes | Yes | Yes | Yes | Yes |
| Horwitz et al ¹⁶ | Yes | Yes | Yes | Yes | Yes | Yes |
| Ogura et al ¹⁷ | Yes | Yes | Yes | Yes | Yes | Yes |
| Jacobsen et al ¹⁸ | Yes | Yes | Yes | Yes | Yes | Yes |

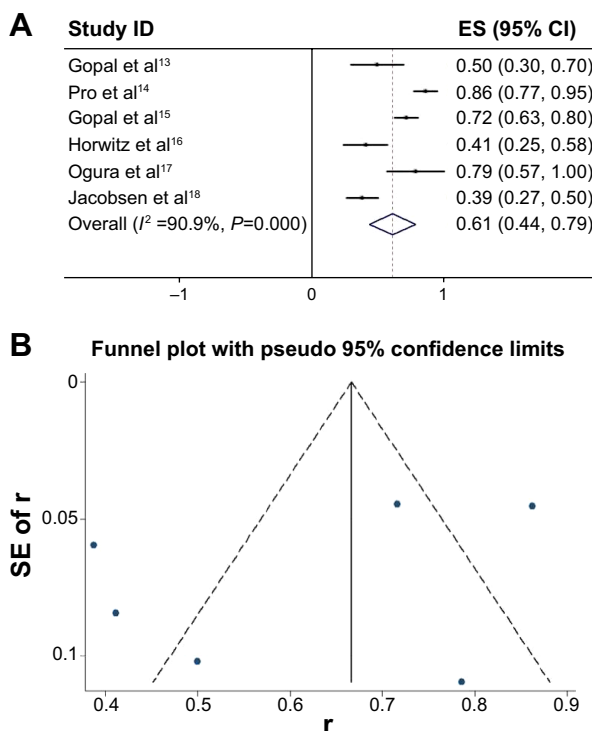


Figure 2 ORR of brentuximab vedotin in patients with relapsed or refractory malignant lymphoma. Objective response rate (A) and funnel plot of selected studies (B).

Note: Weights are from random effect analysis.

Abbreviations: CI, confidence interval; ES, effect size; ORR, objective response rate; SE of r, standard error of regression.

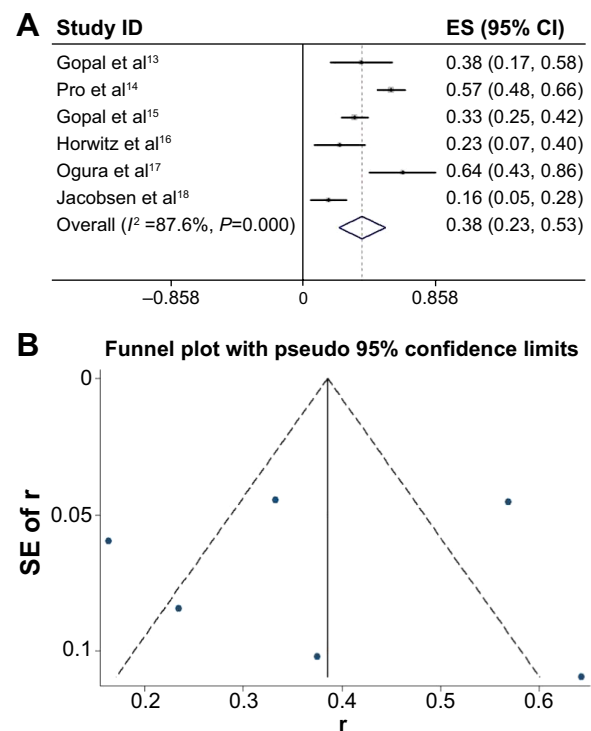


Figure 3 CRR of brentuximab vedotin in patients with relapsed or refractory malignant lymphoma. Complete response rate (A) and funnel plot of selected studies (B).

Note: Weights are from random effect analysis.

Abbreviations: CI, confidence interval; CRR, complete response rate; ES, effect size; SE of r, standard error of regression.

and PRR of brentuximab vedotin in malignant lymphoma. Publication bias within those studies existed, and heterogeneity between studies was also observed. However, the overall results still show that brentuximab vedotin was effective and safe in those patients with malignant lymphomas.

Limitations

Although a number of therapeutic modalities have demonstrated responses, several limitations associated with this meta-analysis were recognized. First, the definition of relapsed and refractory lymphoma varied between investigators, so it was hard to define the indications of choosing brentuximab vedotin as second-line therapy. Second, because of the very limited number of prospective studies of brentuximab vedotin for malignant lymphoma, we had to combine HL, SALCL, T-cell lymphomas, and B-cell lymphomas – we knew that mixing these heterogeneous lymphoma subtypes would make our meta-analysis less valuable, but the final results still showed the effectiveness of brentuximab vedotin in the treatment of relapsed or refractory malignant lymphoma. Third, the precision of pooled effect size was affected by the small sample size

of the included studies, and as a result, we had to choose the random-effects model to increase power and precision regardless of heterogeneity. No RCTs were identified during our literature search, thus, evidence of the efficacy of brentuximab vedotin remained insufficient. Other bias related to our study included the different sponsorships and funding of different studies. So, based on the above, the beneficial role of brentuximab vedotin should be further investigated in the context of larger sample size and randomized trials to document its effect.

Future directions

The conduct of prospective randomized clinical brentuximab vedotin trials to assess the role of brentuximab vedotin in malignant lymphoma would be a hotspot in future research. Understanding more concretely the mechanisms of brentuximab vedotin action in lymphoma will also help guide us in delivering better patient treatment.^{10,19,20}

Conclusion

Our study shows that brentuximab vedotin is an effective and safe treatment for relapsed and refractory malignant lymphoma. In the future, brentuximab vedotin might become

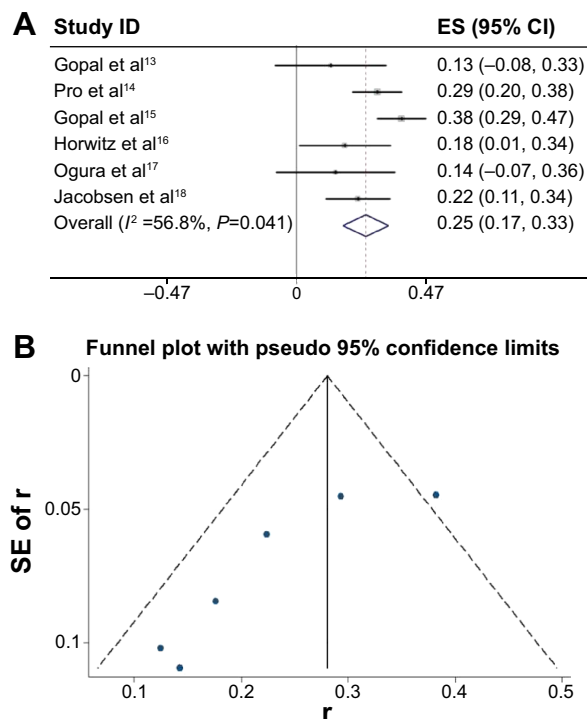


Figure 4 PRR of brentuximab vedotin in patients with relapsed or refractory malignant lymphoma. Partial response rate (**A**) and funnel plot of selected studies (**B**).

Note: Weights are from random effect analysis.

Abbreviations: CI, confidence interval; ES, effect size; PRR, partial response rate; SE of r , standard error of regression.

first-line therapy for relapsed/refractory CD30-positive malignancies, once more clinical trials with larger sample are carried out. The efficacy of brentuximab vedotin combined with chemotherapy or radiotherapy, and strategies for decreasing the toxicity of brentuximab vedotin should also be studied.

Acknowledgment

This work was supported by the National Natural Science Foundation of the People's Republic of China (grant numbers 81170492 and 81370673), National High Technology Research and Development Program 863 of the People's Republic of China (grant number 2012AA022703), National Key Basic Research Program 973 of the People's Republic of China (grant number 2010CB732404), Key Medical Projects of Jiangsu Province (grant number BL2014078), and the Key Discipline of Jiangsu Medicine grant (2011–2015).

Disclosure

The authors report no conflicts of interest in this work.

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