Brentuximab Vedotin effects on prognosis of refractory and relapsed peripheral T-Cell lymphoma: a systematic review

Efeitos do Brentuximabe Vedotin no prognóstico do linfoma de células T refratário e recidivante: uma revisão sistemática

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Abstract

Brentuximab vedotin is a monoclonal anti-CD30 antibody-drug conjugate used to treat some cases of non-Hodgkin lymphoma. In this systematic review, we intend to analyze specifically the brentuximab on the treatment of refractory and relapsed peripheral T-cell lymphoma. Methods: PRISMA protocol for systematic reviews was used. The search was performed on Pubmed, Cochrane and Scielo employing the terms "Brentuximab" and "Peripheral T-cell Lymphoma" from November 2007 to November 2017. The clinical trials were individually assessed by the Cochrane Criteria Score and the systematic reviews by the Quality Assessment of Systematic Reviews and Meta-Analyses Score. Results: Heterogeneous results were found on CD30-positive patients treated with brentuximab vedotin as single-therapy, but the response was better on remission cases and presented longer free-survival time when combined with chemotherapy. Conclusions: Brentuximab vedotin is associated with beneficial results in the treatment of refractory and relapsed peripheral T-cell lymphomas in comparison with front-line therapy.

Keywords: Brentuximab vedotin, peripheral T-cell lymphoma, lymphoma

Resumo

O brentuximabe vedotin é uma droga conjugada de anticorpo monoclonal anti-CD30 usado no tratamento de alguns casos de linfoma não-Hodgkin. Este estudo, desenhado como revisão sistemática, pretende analisar especificamente o uso do brentuximabe no tratamento de linfoma de

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células T refratário e recidivante. Métodos: Foi utilizado o protocolo PRISMA para revisões sistemáticas. A pesquisa foi feita nas bases de dado: Pubmed, Cochrane e Scielo utilizando os termos "Brentuximabe" e "Linfoma de células-T periférico" de novembro de 2007 a novembro de 2017. Os ensaios clínicos foram individualmente avaliados pelo Cochrane Criteria Score e as revisões sistemáticas pelo Quality Assessment of Systematic Reviews and Meta-Analyses Score. Resultados: Foram encontrados resultados heterogêneos em pacientes CD-30 positivos em tratamento com brentuximabe vedotin como terapia única, mas os casos de remissão e tempo de sobrevida foram prolongados quando combinado com quimioterapia. Conclusões: Brentuximabe vedotin apresentou resultados positivos no tratamento de linfoma periférico de célula T refratário/recidivante em comparação com o tratamento de primeira linha.

Palavras-chave: Brentuximabe vedotin, linfoma de célula T periférico, linfoma.

1. Background

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of neoplasms represented by T-cells and natural-killer cells (NK). It accounts for about 5-10% of non-Hodgkin lymphomas (NHL) in Europe and in the United States, and around 15-20% in Asia[1,2]. According to the classification from the World Health Organization of Tumors of Hematopoietic and Lymphoid Tissues, there are three most common histopathologic PTCLs subtypes: peripheral T-cell lymphoma not otherwise specified (30–60%), the angioimmunoblastic T-cell lymphoma and the anaplastic large cell lymphoma (ALCL)[3].

Primary refractory disease and presence of relapses are relatively common[2,4]. Extranodal manifestations, which includes hepatosplenic T-cell lymphoma of γδ origin, enteropathy-associated T-cell lymphoma and subcutaneous panniculitis-like T-cell lymphoma, are rare[1].

PTCL treatment is similar to diffuse large cell lymphoma (DLBCL)[5], once it is a rare disease and to date no effective treatments for any of PTCL subtypes were developed[2,3]. First-line therapy consists in using cyclophosphamide, doxorubicin, vincristine and prednisone. For relapsed and refractory cases, new therapies have been tested as alemtuzumab, brentuximab vedotin (BV), belinostat, pralatrexate and bortezomib[5]. Another treatment option is the chemotherapy with gemcitabine or the combination of gemcitabine, oxaliplatin and dexamethasone, but the response to this therapy was not so positive to majority of patients[6,7]. Stem cell transplantation has also been considered in phase I and phase II studies showing promising results[3,5], except for the fact that many patients do not complete a stable remission of the disease after induction therapy[5].

BV is a conjugate CD-30 monoclonal antibody-drug used to treat some cases of non-Hodgkin lymphomas (i.e. ALCL) and refractory/relapsed PTCL[2]. This drug modifies the transport of the cytotoxic chemoteraphic agent to the malignant cell by linking the anti-CD30 antibody to monomethylauristatin E, which induces cell-cycle switch and, consequently, apoptotic death of the CD30-expressing tumor cell[5,8].

The European Medicines Agency and the US Food and Drug Administration (FDA) approved the use of BV for PTCL. Some studies have been developed analyzing BV as monotherapy compared with the front-line therapy, and with combination of both therapies, but majority are still in phases I or II[5].

2. Objectives

This study aimed to analyze the BV effects on the prognosis of refractory/relapsed PTCL.

3. Methodology

The methods used in this work followed the systematic review process derived from the PRISMA statement. Details of the study protocol are registered on PROSPERO and can be accessed at: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018082354. The full electronic search strategy are available in Appendix.

3.1. Inclusion criteria

3.1.1. Types of studies

Two authors examined the abstract of articles in English, Spanish and Portuguese against the defined inclusion criteria. All potentially relevant full-text articles were retrieved for assessment of quality.

Considering that systematic reviews of clinical trials presents better evidence than systematic reviews of observational studies (which is more appropriate to evaluate the prognosis), and that clinical trials are the most suitable study design to answer therapy questions[9], this paper covered only clinical trials or systematic reviews of clinical trials. All reports about BV treatment in patients diagnosed with refractory/relapsed peripheral T-cell lymphoma were reviewed.

3.1.2. Type of participants

Patients were adults aged at least 18 years with a diagnosis of refractory/relapsed PTCL.

3.1.3. Type of intervention/exposition

For this study, we considered trials in which the intervention consisted in the use of BV alone or in association with classical chemotherapy protocols.

3.1.4. Type of outcome

Modification of PTCL prognosis.

3.2. Exclusion criteria

Studies with sample groups below 10 individuals and in which PTCL was diagnosed but not treated previously (non refractory/non relapsed) were excluded from the study.

3.3. Review criteria

The following databases were consulted: PubMed, Cochrane and Scielo. The search was made using the keywords "Brentuximab" combined with "Peripheral T-cell Lymphoma" according to the databases settings. We considered only studies performed in humans and published in the last ten years, since immunobiological agents on the treatment of PTCL has been developed and better studied in the preceding decade.

3.4. Data extraction and management

The data was extracted by two independent authors using a standard form. This form consisted in a data extraction sheet pilot-test in a sample of five randomly-selected included studies and adjusted accordingly. Disagreements were resolved by discussion between the two review authors; if no agreement could be reached, it was planned a third author would decide.

3.5. Quality assessment

The systematic review quality was assessed by the Quality Assessment of Systematic Reviews and Meta-Analyses Score from the National Heart, Lung and Blood Institute[10]. Acceptable quality was defined as a score of, at least, four of eight points. One point corresponded to an answer "yes" for each criteria (Table 1).

Table 1. Quality assessment of systematic reviews.

Criteria	**Quality rating**	Yang et al [11]
Focused question	**Yes/No/CD, NA or NR†**	Yes
Eligibility criteria	**Yes/No/CD, NA or NR†**	Yes
Comprehensive and systematic approach	**Yes/No/CD, NA or NR†**	Yes
Revision of titles, abstracts, and full-text articles	**Yes/No/CD, NA or NR†**	Yes
Rate from two authors using a standard method	**Yes/No/CD, NA or NR†**	NR
Characteristics and results	**Yes/No/CD, NA or NR†**	Yes
Publication Bias	**Yes/No/CD, NA or NR†**	Yes
Heterogeneity (meta-analyses)	**Yes/No/CD, NA or NR†**	NA

†CD = cannot determine; NA = not applicable; NR = not reported

The clinical trials quality was assessed using the Cochrane Criteria Score. An acceptable quality was defined as a minimum score of 50 points, as shown in Table 2.

Table 2. Quality assessment of clinical studies.

Criteria	Weight Scored Points	Horxwitz et al [12]	Fanale et al [13]	Fanale et al [14]	Prince et al [15]	Zagadail et al [17]
Study Population	(0-25)	12	12	14	16	16
Intervention	(0-25)	15	20	15	15	15
Effect	(0-30)	15	20	25	25	25
Data Presentation and Analysis	(0-10)	10	10	10	10	5
TOTAL	(0-90)	52	62	64	66	61

4. Results

From the initial search (n=60), a total of 16 records were identified and the full-text was screened (Figure 1). Of those, only six articles fulfilled the inclusion criteria: five clinical trials and one systematic review of clinical trials. Table 3 summarizes the findings per study.

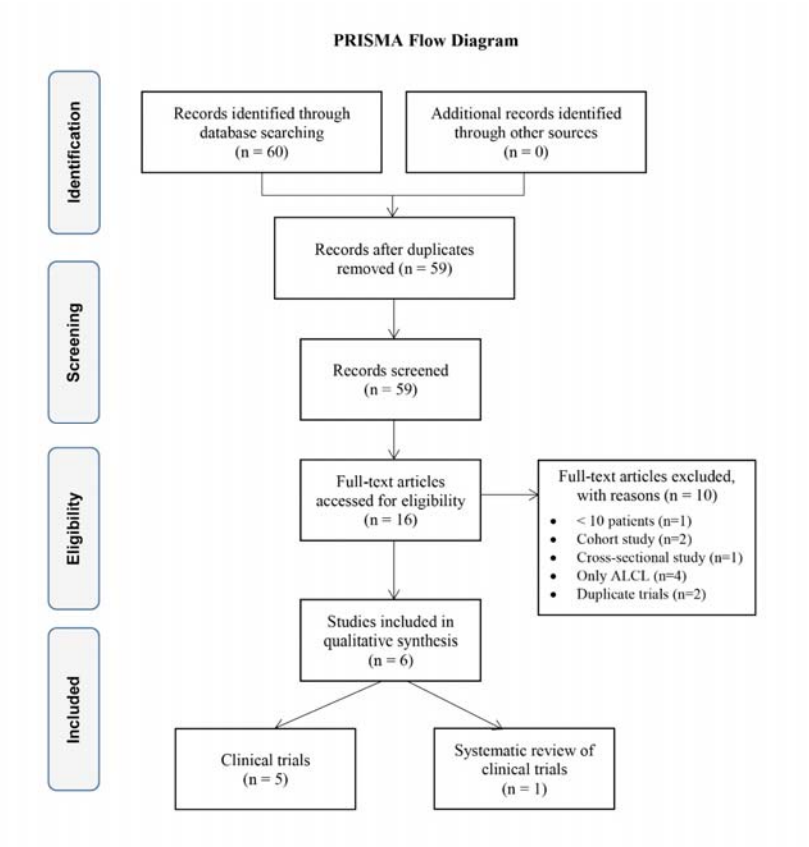

Figure 1. PRISMA flow diagram of the evaluated studies.

Table 3. Summary of the included studies.

Author/Year	Participants	Design of study	Outcome(s)	Result(s)
Yang 2016	618 patients with relapsed/refractory PTCL.	Systematic review.	ORR, DOR, PFS and OS;	ORR: 14-71.5% PFS: 2.6-13.3 months DOR:2.5-16.6 months OS:3.6-14.5 months.
Horwitz 2014	35 patients with MTCL-CD30+/-, of whom 22 PTCL.	Phase 2, open-label, trial.	ORR, DOR, PFS,	ORR: 41% DOR: 7.6 months PFS: 6.7 months
Fanale 2014	39 patients with CD30+ PTCL	Phase 1, open-label, trial	CRR, PFS, OS	CRR: 62-88% PFS: 22.1 months OS: 88% in 1-year
Fanale 2012	39 patients with sALCL	Phase 1, open-label, trial	CRR.	CRR: 88%
Prince, 2017	131 patients with sALCL	Phase 3, open-label, randomised, trial.	PGR	PGR = 53.6%
Fanale 2016	26 patients with CD30+ PTCL	Phase 1 trial.	4-years PFS, OS,	PFS: 52% OS: 80%

ORR = overall response rate, DOR = duration of response; PFS = progression-free survival; OS = overall survival; MTCL-CD30+/- = mature T-cell lymphomas with variable CD30 expression; CRR = complete remission rate; sALCL = systemic anaplastic large cell lymphoma; PGR = proportion of global response.

According to the systematic review published by Yang et al [11], the results were significantly heterogeneous depending on the study even under the same treatment protocol. A cross-sectional analysis of phase II clinical trials demonstrated higher efficacy and safety of BV. This drug was associated with satisfactory results in the treatment of relapsed and refractory PTCL. However, only allogenic stem-cell transplant was adopted as curative therapy, considering that some subjects obtained suitable response prior to chemotherapy.

Horwitz et al analyzed PTCL patients using BV as monotherapy agent in a multicenter study[12]. It recognized that safety of this drug in combination with standard initial chemotherapy, allowing a phase III study for untreated patients with CD30-expressing mature T-cell lymphomas.

Fanale et al. found that individuals under BV monotherapy presented a good response[13]. BV administered sequentially, or combined with chemotherapy, demonstrated a safety profile and exhibited substantial antitumor activity. The maximum BV doses tolerated by the subjects enrolled in both researches did not exceeded 1.8 mg/kg IV in combination with CHP (chemotherapy without vincristine).

The ALCANZA study found a higher disease remission on patients receiving BV (10%) compared to the conventional therapy group (2%). There was also a significant association between BV an the progression-free survival number (16.7 months) versus 3.5 months on the control group [15,16,17]. CHP

protocol associated with BV presented a tolerable safety profile and was associated with long-term remission[18].

5. Discussion

The use of agents targeting the immune system for the treatment of PTCL has been in evidence on the last few years[5]. Studies highlight a positive use of BV in combination with chemotherapy on CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) as well as CHP (cyclophosphamide, doxorubicin and prednisone)[15-18] type in comparison with chemotherapy or BV as single-agents[12-14].

Patients under BV therapy presented a better prognostic with a larger free-survival number on studies analyzed. It may be used on all PCTCL subtypes, as presented by Coiffer. Peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS) was responsible for the highest incidence (25.9%), followed by angioimmunoblastic T-cell lymphoma (AITL) (18.5%) and natural killer/T-cell lymphoma (NKTCL) (10.4%)[5].

Even considering the advances on PTCL treatment using BV and other agents with action on targeting the immune system (as alemtuzumab and lenalidomide), results are still heterogeneous and some opposite options for it uses can be found[19,20]. According with the clinical practice recommendations elaborated by Kharfan-Dabaja et al (2017) the overall quality evidence on cell source (bone marrow or peripheral blood stem cells) and intensity of the disease on use of the agents cited before remains very low[21].

Considering that chemotherapy itself has presented limited effect on refractory/relapsed PTCL patients, some studies defend stem cell transplantation as one of the best therapies improving 4-year progression-free survival of 77% versus 34% from front-line therapy[22], but in many cases chemotherapy can leads patients to have a successful response on stem cell's therapy[20]. Considering the difficulties and limitations on stem cell transplantation, the treatment with BV as second-line therapy needs studies with larger samples and that accompanies patients prognostic with more details, considering its subtypes particularities[3,5,22].

6. Conclusions

The most part of clinical trials evaluating the effects of BV on the prognosis of PTCL are still under execution (phase I or II). However, preliminary results suggests that BV is safe and might be used in combination with classical chemotherapy to improve the clinical outcomes of patients with CD30-positive lymphomas.

7. Financial disclosures and conflicts of interest

The authors declare there are no conflicts of interest. No funding was provided.

8. References

1. Broccoli A, Pier LA, Zinzani L. Peripheral T-cell lymphomas: Focusing on novel agents in relapsed and refractory disease. Cancer Treat Rev. 2017;60(2):120-129.

2. Maruyama D, Nagai H, Maeda Y, Nakane T, Shimoyama T, Nakazato T et al. Phase I/II study of pralatrexate in Japanese patients with relapsed or refractory peripheral T-cell lymphoma. Cancer Sci. 2017; 108(10):2061–2068.

3. Gkotzamanidou M, Papadimitriou CA. Peripheral T-cell lymphoma: The role of hematopoietic stem cell transplantation. Crit Rev Oncol Hematol. 2014; 89(2):248-261.

4. Maruyama D, Nagai H, Maeda Y, Nakane T, Shimoyama T, Nakazato T et al. Phase I/II study of pralatrexate in Japanese patients with relapsed or refractory peripheral T-cell lymphoma. Cancer Sci. 2017; 108(10): 2061–2068.

5. Coiffier B, Federico M, Caballero D, Dearden C, Morschhauser F. Therapeutic options in relapsed or refractory peripheral T-cell lymphoma. Cancer Treat Rev. 2014; 40(9):1080-1088.

6. Reddy NM, Evens AM. Chemotherapeutic Advancements in Peripheral T-Cell Lymphoma. Semin Hematol. 2014; 51(1):17–24.

7. Lamarque M, Bossard C, Contejean A, Brice P, Parrens M, Le Gouill S et al. Brentuximab vedotin in refractory or relapsed peripheral T-cell lymphomas: the french named patient program experience in 56 patients. Haematologica. 2016; 101(3):103–106.

8. Yasenchak CA, Halwani A, Advani R, Ansell S, Budde LE, Burke JM et al. Brentuximab Vedotin with RCHOP as frontline therapy in patients with high-intermediate/high-risk diffuse large B cell lymphoma (DLBCL): results from an ongoing phase 2 study. Blood. 2015; 126(23):612-633.

9. Burns PB, Rohrichand RJ, Chung KC. The Levels of Evidence and their role in Evidence-Based Medicine. Plast Reconstr Surg. 2011; 128(1):305-310.

10. National Heart, Lung, and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults - the evidence report. 98th ed. US: Bethesda, 1998.

11. Yang YT, Tai CJ, Chen C, Wu HC, Mikhaylichenko N, Chiu HT et al. Highly diverse efficacy of salvage treatment regimens for relapsed or refractory peripheral T-cell lymphoma: a systematic review. PLoS One. 2016; 11(10):132-144.

12. Horwitz SM, Advani RH, Bartlett NL, Jacobsen ED, Sharman JP, O'Connor OA et al. Objective responses in relapsed T-cell lymphomas with single-agent brentuximab vedotin. Blood. 2014;123(20): 3095–3100.

13. Fanale MA, Horwitz SM, Forero-Torres A, Bartlett NL, Advani RH, Pro B et al. Brentuximab vedotin in the front-line treatment of patients with CD30+ peripheral T-cell lymphomas: results of a phase I study. J Clin Oncol. 2014; 32(28):3137–3143.

14. Fanale MA, Shustov AR, Forero-Torres A, Bartlett NL, Advani RH, Pro B et al. Brentuximab vedotin administered concurrently with multi-agent chemotherapy as frontline treatment of ALCL and other CD30-positive mature T-cell and NK-cell lymphomas. Blood. 2012; 120(1):35-58.

15. Prince HM, Kim YH, Horwitz SM, Dummer R, Scarisbrick J, Qauglino P et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet. 2017; 390(10094):555-566.

16. Prince HM, Dummer R, Whittak S, Horwitz S, Duvic M, Scarisbrick J, et al. Patient-reported outcomes and quality of life in patients with cutaneous T cell lymphoma: results from the phase 3 alcanza study. 2017; 35(Suppl S2):247–248.

17. Zagadailov E, Prince HM, Whittaker S et al. Phase 3 alcanza study of brentuximab vedotin (BV) or physician's choice (PC) of methotrexate (MTX) or bexarotene (BEX) in CD30-positive cutaneous t-cell lymphoma (CTCL): number needed to treat analysis. Eha. 2017; 19(4):181-204.

18. Fanale MA, Horwitz SM, Forero-Torres A, Bartlett NL, Advani, RH, Pro B et al. Four-year survival and durability results of brentuximab vedotin in combination with CHP in the frontline treatment of patients with CD30-expressing peripheral T-cell lymphomas. Blood. 2016; 128(22):429-453.

19. Aoyama Y, Kodaka T, Zushi Y, Goto Y, Tsunemine H, Itoh T et al. Composite lymphoma as co-occurrence of advanced chronic lymphocytic leukemia/small lymphocytic lymphoma carrying trisomy 12 and t(14;18) and peripheral T-cell lymphoma. J Clin Exp Hematop. 2018; 12(1):27-31.

20. Ma H, Davarifar A, Amengual JE. The future of combination therapies for peripheral T cell lymphoma (PTCL). Curr Hematol Malig Rep. 2018; 13(1):13-24.

21. Kharfan-Dabaja MA, Kumar A, Ayala E, Hamadani M, Reimer P, Gisselbrecht C et al. Clinical practice recommendations on indication and timing of hematopoietic cell transplantation in mature T cell and NK/T cell lymphomas: an international collaborative effort on behalf of the guidelines committee of the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2017; 23(11):1826-1838.

22. Feldman T, Farber CM, Choi K, Faria C, Goy A, Connors J et al. Treatment of Peripheral T-cell lymphoma in community settings. Clin Lymphoma Myeloma Leuk. 2017; 17(6):354-361.