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Brentuximab vedotin for treatment of non-Hodgkin lymphomas: A systematic review

Garrett K. Berger^{a,1}, Ali McBride^{a,1}, Stephanie Lawson^a, Kelsey Royball^a, Seongseok Yun^b, Kevin Gee^c, Irbaz Bin Riaz^b, Ahlam A. Saleh^d, Soham Puvvada^{b,2}, and Faiz Anwer^{e,*},²

^aCollege of Pharmacy, University of Arizona, Tucson, AZ, 85721, United States

^bDepartments of Medicine, University of Arizona, Tucson, AZ, 85721, United States

^cCollege of Medicine, University of Arizona, Tucson, AZ, 85721, United States

^dUniversity of Arizona Health Sciences Library, University of Arizona, Tucson, AZ 85721, United States

^eHematology, Oncology, Blood & Marrow Transplantation, Department of Medicine, University of Arizona, Tucson, AZ, 85721, United States

Abstract

Background—Brentuximab vedotin (BV) is an antibody-drug conjugate (ADC) comprising a CD30-directed antibody, conjugated to the microtubule-disrupting agent MMAE via a protease cleavable linker. BV is FDA approved for use in relapsed classical Hodgkin lymphoma (HL) and relapsed systemic anaplastic large cell lymphoma (sALCL). There are multiple publications for its utility in other malignancies such as diffuse large B-cell lymphoma (DLBCL), mycosis fungoides (MF), Sézary syndrome (SS), T-cell lymphomas (TCL), primary mediastinal lymphoma (PMBL), and post-transplant lymphoproliferative disorders (PTLD). We believe that BV could potentially provide a strong additional treatment option for patients suffering from NHL.

Objective—Perform a systematic review on the use of BV in non-Hodgkin lymphoma (NHL) and other CD30⁺ malignancies in humans.

Data sources—We searched various databases including PubMed (1946–2015), EMBASE (1947–2015), and Cochrane Central Register of Controlled Trials (1898–2015).

Eligibility criteria—Inclusion criteria specified all studies and case reports of NHLs in which BV therapy was administered.

*Corresponding author at: Department of Medicine, Division of Hematology Oncology, University of Arizona Cancer Center, 1501 N Campbell Ave, Tucson, AZ 85721, United States. anwerf@email.arizona.edu, mhalajia@email.arizona.edu (F. Anwer).

¹G.K.B and A.M. equally contributed as first co-authors

²FA and SP equally contributed as last co-authors

Declaration of interests

Dr. McBride discloses financial interest from Seattle Genetics in the form of advisory board membership.

Dr. Puvvada discloses financial interest from Genentech, Abbvie, Spectrum, Janssen, Takeda and Seattle Genetics in the form of institutional research funding, travel for investigators' meetings and advisory board memberships.

Dr. Anwer discloses financial interest from Seattle Genetics and Incyte Corporation in the form of advisory board membership and participation in speakers' program.

All other authors have nothing to disclose.

Included studies—A total of 28 articles met these criteria and are summarized in this manuscript.

Conclusion—Our findings indicate that BV induces a variety of responses, largely positive in nature and variable between NHL subtypes. With additional, properly powered prospective studies, BV may prove to be a strong candidate in the treatment of various CD30⁺ malignancies.

Keywords

Brentuximab vedotin; Relapse or refractory NHL; CD30

1. Introduction

CD30 (Ki-1) is a cell membrane protein deriving from the tumor necrosis factor (TNF) receptor family. Expression of CD30 is correlated with B and T cell activation. Since its initial description in the early 1980's, the CD30 antigen has been associated primarily with Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL) (Stein et al., 1982). CD30 expression is restricted to a small population of activated B and T lymphocytes, NK cells, and lower levels in activated monocytes and eosinophils (Argrawal et al., 1996). In addition to sALCL, the CD30 antigen has been identified in various other non-Hodgkin lymphomas (NHL) including hematological malignancies such as diffuse large B-cell lymphoma (DLBCL), T-cell lymphomas (TCL), primary mediastinal lymphoma (PMBL), post-transplant lymphoproliferative disorders (PTLD), enteropathy associated PTCL, cutaneous malignancies such as mycosis fungoides (MF), Sézary syndrome (SS), and lymphoid papulosis (LyP) (Stein et al., 1982; Jacobsen et al., 2015; Kim et al., 2014; Schwarting et al., 1989). The CD30 antigen also has been identified in non-lymphomatous malignancies like germ cell tumors such as embryonal carcinoma, seminomas, malignant melanomas, neoplasms of mesenchymal origins including leiomyomas, leiomyosarcomas, rhabdomyosarcomas, aggressive fibromatoses, fibrosarcomas, synovial sarcomas, giant cell tumors of tendon sheaths, malignant fibrous histiocytomas, osteosarcomas, Ewing's sarcomas, in a tumor cell subpopulation of malignant schwannomas, in the Schwann cell compartment of ganglioneuromas, and in the myoepithelial compartment of fibroadenomas, inflammatory myofibroblastic tumors, ovarian cancer, mesothelioma, squamous cell carcinoma, triple negative breast cancer, pancreatic cancer, small cell lung cancer, anal cancer, thyroid carcinoma, cutaneous angiosarcoma, and a small subset of undifferentiated nasopharyngeal non-keratinizing carcinoma (Latz et al., 1995; Gopalan et al., 2009; Dürkop et al., 2000; Pallesen and Hamilton-Dutoit, 1988; Polski and Janney, 1999; Lau et al., 2007; Suster et al., 1998; Bode et al., 2011; Hittmair et al., 1996; Sharman et al., 2012; Garcia-Prats et al., 1998; Dunphy, 2000; Aggerholm-Pedersen et al., 2011; Weed and Folpe, 2008; Kneile et al., 2006; Menasce and Eyden, 2005; Mechttersheimer and Moller, 1990; Mariño-Enríquez et al., 2016). Moreover, systemic mastocytosis, which is classified as a myeloid neoplasm, is also known to express CD30 although the clinical data is limited (Borate et al., 2016).

In NHL, CD30 has been utilized as a therapeutic target (Ferri, 2015; Terada and Sugiura, 2010; Muta and Podack, 2013). Brentuximab vedotin is an ADC comprising a CD30-directed antibody, conjugated to the microtubule-disrupting agent MMAE via a protease

cleavable linker. It received accelerated approval from the federal drug administration (FDA) in 2011 for the treatment of relapsed classical HL and sALCL (Brentuximab vedotin, 2011).

Based on clinical benefit observed in HL and sALCL, the efficacy of BV also has been tested in many other NHLs that express CD30. In this systematic review, our objective is to summarize data from phase I/II trials along with case reports, case series and meeting abstracts that focus on the use of BV in treatment of CD30⁺ NHLs.

2. Materials and methods

2.1. Eligibility criteria

Inclusion criteria specified all studies and case reports of NHLs in which BV therapy was administered. Studies with HL, non-human populations, and no reported objective response outcome were excluded from the systematic review (Fig. 1).

2.2. Literature search

A literature search was performed in the following resources: PubMed (1946–2015); [Embase.com](#) EMBASE (1947–2015); Wiley Cochrane Library- Central Register of Controlled Trials (1898–2015); Thompson Reuters Web of Science- Science Citation Index Expanded (1900–2015); Thompson Reuters Web of Science-Conference Proceedings Citation Index-Science (1990–2015); Scopus (1823–2015). Additionally, the following clinical trial registers were searched: [ClinicalTrials.gov](#) and the World Health Organization International Clinical Trials Registry Platform (ICTRP). The search strategies included various combinations of text-words, and controlled vocabulary when available. There were no language or year limits placed on the search. Database and trial register searches were conducted on 5/22/2015. The detailed search strategy is provided in the Appendix 1. The following conference proceedings were searched for relevant abstracts: the American Society of Hematology (from 2000), the American Society of Clinical Oncology (from 2000), the European Hematology Association (from 2000), the American Society of Bone Marrow Transplantation (from 2000), and the European Society of Medical Oncology (from 2000) last assessed 6/30/2015. Also, the references from all identified studies were investigated manually to identify relevant trials.

2.3. Study selection

The titles and abstracts of screened articles were reviewed independently by three reviewers (G.K.B., S.L., K.R.). Full articles that were potentially relevant to study were reviewed with the original three reviewers in addition to the fourth reviewer (K.G.) to confirm the eligibility. Any discrepancies were resolved after group discussion with the four aforementioned reviewers.

2.4. Data abstraction and analysis

Studies were identified by the first author and year of first full publication (if available) or published abstract or letter. Outcomes and timing of reported outcomes were recorded as specified in each study. When not explicitly stated, outcomes were calculated on the basis of information included within the published record; if this was not possible, 'not reported' was

recorded in the results tables. Data are presented as the mean ($\pm$ standard deviation) or median (range), and all values are expressed to one decimal place unless the original article did not provide this degree of accuracy. Primary study outcomes focus on therapeutic efficacy of BV in the treatment of NHLs using objective response rate (ORR) as a measure.

3. Results

3.1. Search results

The systematic search identified a total of 2753 records. Additionally, 43 records were screened from the WHO ICTRP search. After excluding 1110 duplicates, the remaining 1686 records were screened for relevance based on their titles and abstracts. Of these 1686, 73 were deemed potentially eligible and retrieved for full text review. After detailed review, a total of 46 records were further excluded for the following reasons: duplicate study data ($n = 39$), ongoing trials with no available data ($n = 6$), and not focused on BV ($n = 1$). A total 27 articles met our inclusion criteria: phase II ($n = 7$), phase I ($n = 6$), phase I/II ($n = 1$) and case reports ($n = 13$). The summary of the selection process is depicted in the flow diagram (Fig. 1). At a later date, we decided to include mastocytosis and germ cell tumor data yielding one additional case study and one additional phase II study.

3.2. Study demographics

All selected studies included patients with pathologically proven NHLs and our systematic review included a total 359 patients of sALCL ($n = 124$), primary cutaneous ALCL ($n = 6$), DLBCL ($n = 61$), PMBL ($n = 6$), grey zone lymphoma (GZL) ($n = 7$), follicular lymphoma (FL) ($n = 3$), plasmablastic lymphoma ($n = 2$), peripheral TCL ($n = 45$), PTLT ($n = 10$), MF ($n = 79$), SS ($n = 13$), LyP ($n = 9$), germ cell tumors (GCT) ($n = 3$) and mastocytosis (MC) ($n = 4$).

4. Group A: B-cell malignancies

1. DLBCL

There are two phase II studies totaling 61 patients with DLBCL.

1.1 Phase II studies—Jacobsen et al. performed a phase II study with relapsed/refractory DLBCL (Jacobsen et al., 2015). Of the 49 patients in this study, 57% were male ($n = 28$) (median age 62 years). These patients displayed variable levels of CD30 expression. An objective response (OR) to BV was shown in 43% ($n = 21$) with a median duration of 22.4 weeks. Complete remission (CR) was obtained by 17% ($n = 8$) (median duration, 66.4 weeks) and 27% ($n = 13$) achieved a partial response (PR). Stable disease (SD) was maintained in 22% ($n = 11$) and 33% ($n = 16$) experienced disease progression (PD). Sixteen additional patients were given BV with rituximab and displayed favorable tolerance for this therapy (Jacobsen et al., 2015). The Yasenchak et al. phase II study utilized BV in combination with standard R-CHOP chemotherapy for the front-line treatment of patients with CD30-unselected high-intermediate/high-risk DLBCL. Twelve patients reached end of therapy (33 enrolled). The median age was 66 years. An OR was shown in 92% ($n = 11$) (Yasenchak et al., 2014). Complete remission was achieved by 58% ($n = 7$) and 33% ($n = 4$)

achieved PR. Progressive disease was experienced by 9% ($n = 1$). Duration of response data not available at this time.

2. Post-Transplant Lymphoproliferative Disorder (PTLD)

There is one phase I and one phase II study for patients with PTLD, along with one case report for a total of ten patients.

2.1 Phase I studies—Gandhi et al. published a phase I/II trial looking at BV in adult PTLD patients with previously untreated CD20⁺ NHL, with co-expression of EBV and/or CD30 (all at any level) (Gandhi et al., 2014). Of the six patients, one was polymorphic (CD30⁺, EBV⁺), four were monomorphic B-cell like (all CD30⁺) and one was TCL (CD30⁻, EBV⁺). Median age was 61 years, 33% ($n = 2$) were male, and median follow-up was nine months. Five patients (71%) had a CR and none of them showed PD. One patient with SD achieved CR after discontinuing protocol chemoimmunotherapy (CIT). One patient who achieved SD declined further therapy, but had not progressed at his last follow up (Gandhi et al., 2014).

2.2 Phase II studies—In the Jacobsen et al. phase II study of relapsed/refractory DLBCL, three of study subjects had CD30⁺ PTLD (Jacobsen et al., 2015). Age and gender data are not available for these patients. An OR was experienced by 33% ($n = 1$), 33% ($n = 1$) achieved CR, and 33% ($n = 1$) experienced PD (Jacobsen et al., 2015).

2.3 Case reports—Hill et al. described a PTLD in a 62-year-old female with CD30⁺ DLBCL, who achieved CR for a duration of 20 weeks follow-up (Hill et al., 2014).

3. Grey Zone Lymphoma (GZL)

There is one phase II study and one case report totaling seven patients with GZL.

3.1 Phase II studies—The Jacobsen et al. phase II study included a total of six GZL patients (Jacobsen et al., 2015). All patients ($n = 6$) were CD30⁺. Gender and age data are not available for this subset of patients. An OR was shown in 50% ($n = 3$). Seventeen percent ($n = 1$) attained CR and 33% ($n = 2$) experienced PR. Stable disease was maintained by 33% ($n = 2$) and 17% ($n = 1$) experienced PD to single agent BV (Jacobsen et al., 2015).

3.2 Case reports—Ponugupati et al. detailed a case report of a 62-year-old male with relapsed CD30⁺, CD20⁺, ALK⁻ GZL (Ponugupati and Haddad, 2012). He was treated with rituximab followed by BV along with bendamustine, and achieved CR after three cycles (nine weeks) (Ponugupati and Haddad, 2012).

4. Primary Mediastinal B-Cell Lymphoma (PMBL)

There is one phase II study totaling six patients with PMBL.

4.1 Phase II studies—A total of six relapsed CD30⁺ PMBL patients were included in Jacobsen et al. phase II study. Age and gender data are not available for this subset.

Seventeen percent (n = 1) experienced an OR. CR was achieved by 17% (n = 1). SD was maintained by 50% (n = 3) and 33% (n = 2) experienced PD (Jacobsen et al., 2015).

5. Follicular Lymphoma (FL)

There is one phase II study totaling three patients with FL.

5.1 Phase II studies—In the Jacobsen et al. phase II study, three patients had a diagnosis of CD30⁺ FL. Age and gender data are not reported for this subset. 0% (n = 0) showed an OR. SD was maintained by 66% (n = 2) and 33% (n = 1) experienced PD (Jacobsen et al., 2015).

5. Group B: T-cell malignancies

1. Systemic Anaplastic Large Cell Lymphoma (sALCL)

There are five phase I, three phase II studies, and three case reports totaling 124 patients with sALCL.

1.1 Phase I studies—The Younes et al. phase I study looked at CD30⁺ relapsed HL (n = 42), angioimmunoblastic TCL (n = 1) and sALCL (n = 2) patients treated with BV (Younes et al., 2010). No gender or age data are specified for these patients. CD30 positivity was seen in 100% (n = 2) and 100% (n = 2) were ALK⁺. All patients (n = 2) achieved CR (median duration 36 weeks) (Younes et al., 2010). In the Gibb et al. phase I study, refractory CD30⁺ lymphoma patients were treated with BV as a bridge to allogeneic SCT (Gibb et al., 2013). Of the 24 patients in this study, 18 had HL, five had sALCL and one had TCL. Gender and age data are not specified for this subset of patients. CD30 positivity was seen in 100% (n = 5), 40% (n = 2) were ALK⁺, and 60% (n = 3) had unknown ALK status. Complete remission leading to transplant was achieved by 60% (n = 3). Data is not available for the remaining two patients regarding SD versus PD (Gibb et al., 2013). The Fanale et al. phase I trial studied the efficacy of BV as a front-line treatment in peripheral TCL patients including sALCL (n = 32) (Fanale et al., 2014). Of the 32 patients, 50% (n = 16) were male (median age of 35 years). CD30 positivity was seen in 100% (n = 32) and 19% (n = 6) were ALK⁺. An OR was experienced by 94% (n = 30) (median duration 52.8 weeks). Of these patients, 75% (n = 24) achieved CR (median duration 105.2 weeks) and 19% (n = 6) experienced a PR. Progressive disease was suffered by 6% (n = 2) (Fanale et al., 2014). Bartlett et al. published a phase I dose-escalation study (Bartlett et al., 2009). Four patients had sALCL. There are no available data separating the gender and age for this subset of patients. CD30 positivity was seen in 100% (n = 4). There were no available ALK expression data. Complete remission was achieved by 75% (n = 3) (median duration N/A). The remaining 25% (n = 1) experienced SD (Bartlett et al., 2009). Fanale et al. published a phase I dose-escalation study with refractory HL (n = 38), sALCL (n = 5) and peripheral T-cell lymphoma (PTCL) (n = 1) (Fanale et al., 2012). There are no available data separating the gender and age for this subset of patients. CD30 positivity was seen in 100% (n = 5) and 20% (n = 1) were ALK⁺. An OR was experienced by 80% (n = 4) (median duration N/A). Complete remission was achieved by 80% (n = 4) (median duration N/A) and 20% (n = 1) experienced SD (Fanale et al., 2012).

1.2. Phase II studies—The Pro et al. phase II study included 58 relapsed/refractory sALCL patients of which 57% (n = 33) were male and the median age was 52 years (Pro et al., 2012). CD30 positivity was seen in 100% (n = 58) and 72% (n = 42) were ALK⁺. An OR was experienced by 86% (n = 50) (median duration 50.4 weeks). Fifty seven percent (n = 33) achieved CR (median duration 52.8 weeks) and 29% (n = 17) experienced a PR. Stable disease was maintained by 3% (n = 2) and 5% (n = 3) experienced PD (Pro et al., 2012). In the Ogura et al. phase I/II study looking at CD30⁺ patients with HL (n = 14) or sALCL (n = 5), 100% (n = 5) were male (median age 41 years) (Ogura et al., 2014). The CD30 biomarker was expressed in 100% (n = 5) and 20% (n = 1) were ALK⁺. Of these patients, 100% (n = 5) experienced an OR (median duration 38.80 weeks). Eighty percent (n = 4) achieved CR (median duration N/A) and 20% (n = 1) achieved a PR (Ogura et al., 2014). In the Bartlett et al. phase II study looking at retreatment of CD30⁺ patients with HL (n = 21) or sALCL (n = 8) who initially achieved an OR with BV, the median age of sALCL patients was 51.5 years and male patients made up 50% (n = 4) (Bartlett et al., 2014a). All sALCL patients were CD30⁺ (n = 8) and 38% (n = 3) of them were ALK⁺. An OR was experienced by 88% (n = 7) (median duration 28 weeks). Five patients (63%) achieved CR (median duration 20 weeks) and 25% (n = 2) experienced PR (Bartlett et al., 2014a).

1.3 Case reports—Sampson et al. reported a 17-year-old male patient with CD30⁺ sALCL (no ALK data is available) who relapsed after autologous transplant (Sampson et al., 2012). The patient obtained CR immediately, which lasted up to 69 weeks of follow-up. Heidegger et al. reported a case of 24-year-old male with CD30⁺ and ALK⁺ sALCL relapsed/refractory after CHOP therapy (Heidegger et al., 2014). A combination of BV and DHAP was administered as a salvage regimen. The patient achieved CR for three consecutive weeks leading to HSCT (Heidegger et al., 2014). Broccoli et al. detailed two cases of sALCL (Broccoli et al., 2013). A 65-year-old male with CD30⁺ and ALK[−] relapsed sALCL achieved PR after first treatment and CR after third cycle (nine weeks). At last follow-up, the patient was still in CR (duration 36 weeks). The second case was a 73-year-old female with CD30⁺ ALK[−] relapsed/refractory sALCL. After three cycles of BV (12 weeks), the patient experienced notable drug-induced peripheral neuropathy and BV was discontinued. At a follow-up of 40 weeks, the patient was in CR (Broccoli et al., 2013).

2. Sézary Syndrome (SS)/Mycosis Fungoides (MF)

There are three phase II studies and four case reports totaling 91 patients with MF (n = 79) and SS (n = 13).

2.1 Phase II studies—Bashey et al. published a phase II abstract detailing BV in the treatment of MF (n = 14) and SS (n = 1) with variable CD30 expression (Bashey et al., 2012). Median age was 64 years. Gender data are not available. An OR was observed in 60% (n = 9) (not specified CR versus PR). Median duration is unknown. Of the patients who did not experience an OR, the data do not specify SD versus PD. Kim et al. published a phase II study observing BV in 22 patients with MF and 10 patients with SS (Kim et al., 2014). CD30 expression was variable. Gender differentiating data are not available. The median age was 62-years-old. An OR was experienced by 70% (n = 21) in which CR was achieved by 3% (n = 1; SS) and 66% (n = 20) experienced PR. Stable disease was

maintained by 13% (n = 4) and 17% (n = 5) experienced PD. Duvic et al. published a phase II study observing BV activity in CD30⁺ cutaneous TCL and lymphoproliferative disorders (Duvic et al., 2013). Of the 48 total patients, there were 28 with CD30⁺ MF and seven with CD30⁺ MF with LyP. Gender and age information are not specified for these subpopulations. Of these patients, 60% (n = 21) achieved an OR (median duration 14-4 weeks). Eight patients (23%) achieved CR (median duration not reported) and 37% (n = 13) experienced a PR.

2.2 Case reports—Devarakonda et al. detailed a case report regarding a male (age not reported) with relapsed CD30⁺ MF (Devarakonda and Haddad, 2012). This patient achieved CR after three cycles (nine weeks) and continued for two more cycles at time of publication. Mehra et al. detailed a case report of four patients with MF/SS (Mehra et al., 2015). Three patients had MF and one had SS. Three-quarters (n = 3) were male (median age 50.5 years). All patients (n = 4) were CD30⁺. An OR was observed in 50% (n = 2). Twenty-five percent (n = 1) achieved CR and 25% (n = 1) experienced a PR. These patients promptly received allogeneic HSCT. The patient who experienced the CR was still in CR 32 weeks after transplantation. The patient who experienced PR relapsed after transplantation and eventually expired. One patient (25%) experienced PD and later expired. Mody et al. detailed two case reports of male patients with CD30⁺ MF (Mody et al., 2013). Both patients were male (75 years and 87 years). Both patients achieved CR for a median duration of 27 weeks. Saintes et al. detailed two case reports of BV use in relapsed/refractory MF/SS (Saintes et al., 2015). One of a male patient with CD30⁺ MF and one of a male patient with CD30⁺ SS. Age data were not available. Both patients experienced a PR for a median duration of 31.5 weeks.

3. Peripheral T-cell lymphoma/Angioimmunoblastic T-cell lymphoma

3.1 Phase I studies—There are four phase I studies totaling 10 patients with PTCL. Younes et al. published a phase I study and one patient in this study had a diagnosis of CD30⁺ angioimmunoblastic TCL (Younes et al., 2010). Age and gender of this patient are not detailed separately. This patient experienced PD. Of note, this patient had the best response of those in the low dose cohort. Gibb et al. published a phase I study looking at BV as bridge therapy for allogeneic SCT in patients with HL, ALCL or CD30⁺ TCL (Gibb et al., 2013). One patient in this study had CD30⁺ TCL. The age and gender of this patient are not detailed separately. This patient experienced either PD or death prior to follow-up PET after 4 cycles (1 of 4 in this category; results not specific to TCL). Fanale et al. published a phase I study looking at BV as front-line therapy for patients with TCL (Fanale et al., 2014). Seven patients fall into the category of PTCL [PTCL-NOS (n = 2), angioimmunoblastic TCL (n = 2); enteropathy associated TCL (n = 1), TCL (n = 2)]. Of these patients, 14% (n = 1) were male (median age 55 years). All patients (n = 7) were CD30⁺. An OR was observed in 100% (n = 7) of patients (median duration 56.7 weeks). All patients (n = 7) achieved CR as well (median duration 56.7 weeks). An additional phase I study performed by Fanale et al. details one patient, diagnosed with CD30⁺ TCL, who experienced a PR for an unknown duration (Fanale et al., 2012).

3.2. Phase II studies—Horwitz et al. published a phase II study observing BV efficacy in relapsed TCL (Horwitz et al., 2014). This study included a total of 35 patients with PTCL (PTCL-NOS [n = 22], angioimmunoblastic TCL [n = 13]). Males comprised 77% (n = 27) (median age 64 years). All of these patients were CD30⁺. An OR was observed in 41% (n = 14) (median duration 30.4 weeks). Complete remission was achieved in 24% (n = 8) (median duration 30.4 weeks) and 18% (n = 6) experienced a PR. Stable disease was maintained in 18% (n = 6) and 41% (n = 14) experienced PD.

4. Lymphatoid Papulosis (LyP)

4.1 Phase II studies—Duvic et al. published a phase II study observing BV activity in CD30⁺ cutaneous TCL and lymphoproliferative disorders (Duvic et al., 2013). Of the 48 total patients, there were nine with CD30⁺ LyP alone. Gender and age information are not specified for this subpopulation. All of these patients (n = 9) achieved an OR (median duration 23 weeks). Complete remission was achieved by 56% (n = 5) and 44% (n = 4) experienced a PR.

5. Primary Cutaneous ALCL

There is one phase II study and two case reports totaling six patients with primary cutaneous ALCL (pc-ALCL).

5.1. Phase II studies—Duvic et al. published a phase II study observing BV activity in CD30⁺ cutaneous TCL and lymphoproliferative disorders (Duvic et al., 2013). Of the 48 total patients, there were two with CD30⁺ pc-ALCL and two with CD30⁺ pc-ALCL and LyP. Gender and age information are not specified for these sub-populations. All of these patients (n = 4) achieved an OR (median duration 18 weeks). All four patients achieved CR (median duration 10 weeks).

5.2. Case reports—Patsinakidis et al. detailed a case report of a 56-year-old male with CD30⁺ and ALK⁻ pc-ALCL (Patsinakidis et al., 2015). The patient achieved PR after four weeks and CR after another four weeks. No follow-up data is available. Kaffenberger et al. detailed a case report of a 60-year-old male with CD30⁺, ALK⁻ refractory pc-ALCL (Kaffenberger et al., 2013). After two cycles (six weeks) the patient experienced CR, which continued through follow-up at 56 weeks.

6. Group C: other malignancies

1. Plasmablastic Lymphoma

There is one phase II study and one case report totaling two patients with plasmablastic lymphoma (PBL).

1.1. Phase II studies—A phase II study reported one patient with CD30⁺ PBL, who achieved PD upon BV treatment (Jacobsen et al., 2015)

1.2 Case reports—Holderness et al. detailed a case report of a 48-year-old male with transformed CLL (PBL) with a CD30 positive immunophenotype. After failure of two

intensive regimens, BV therapy induced a significant decrease in the size of the supraclavicular lesion over the following 72 h, although the patient expired from a significant GI bleed (Holderness et al., 2013).

2. Germ Cell Tumors (GCT)

CD30 positivity is seen in germ cell tumors **5** (Dürkop et al., 2000; Pallesen and Hamilton-Dutoit, 1988; Hittmair et al., 1996; Chiarle et al., 1999; Leroy et al., 2002). There is one phase II study totaling three patients with germ cell tumors. There is a need for studies both in the pre-clinical and clinical settings (Sharman et al., 2012).

2.1 Phase II studies—Albany et al. published a phase II abstract evaluating BV activity in CD30⁺ non-lymphomatous malignancies (Albany et al., 2013). Of the 84 total enrolled patients, there were three with CD30⁺ relapsed or refractory testicular cancer. All three patients were male with a median age of 26 years. Two of these patients (66%) achieved an OR (median duration NR), both of which were PRs. One patient (33%) experienced SD (median duration NR).

3. Mastocytosis

3.1 Case reports—Borate *et al.* details four patients with aggressive or indolent systemic mastocytosis (SM) (Borate et al., 2016). All patients (n = 4) were CD30 positive, and 75% (n = 3) were male (median age 63 years). One patient (25%) experienced PR (median duration 144 weeks), one patient showed SD (25%), and two patients (50%) had no response. There is a need for further studies in both the pre-clinical and clinical settings.

7. Summary

DLBCL

There are 61 CD30⁺ patients in two phase II studies. An OR was experienced by 52% (n = 32), and 25% (n = 15) achieved CR. A PR was experienced by 28% (n = 17), 18% (n = 11) maintained SD and 28% (n = 17) experienced PD.

PTLD

There are ten patients over one phase I study, one phase II study and one case report. All patients (n = 9) were CD30⁺. Of these patients, 56% (n = 5) experienced an OR (median duration 36 weeks). Complete remission was achieved by 56% (n = 5) (median duration 36 weeks), 22% (n = 2) maintained SD and 11% (n = 11) experienced PD.

GZL

There are seven patients over one phase II study and one case report. All patients (n = 7) were CD30⁺. Of these, 57% (n = 4) experienced an OR (median duration not segregated for these respective studies). Complete remission was achieved by 29% (n = 2), 29% (n = 2) experienced PR, 29% (n = 2) maintained SD and 14% (n = 1) experienced PD.

PMBL

There is one phase II study totaling six patients. CD30 positivity was seen in 100% (n = 6). Of these, 17% (n = 1) experienced an OR. Complete remission was achieved in 17% (n = 1), 50% (n = 3) maintained SD and 33% (n = 2) experienced PD.

FL

There is one phase II study totaling three patients with FL (Jacobsen et al., 2015). All of these patients (n = 3) were CD30⁺. No patients experienced an OR, 66% (n = 2) maintained SD and 33% (n = 1) experienced PD.

ALCL

There are 123 patients over eight phase I and phase II studies, in addition to three case reports. CD30 positivity was seen in 100% (n = 123) with variable expression while 48% (n = 56) were ALK⁺. An OR was seen in 87% (n = 108) of these patients (median duration 41.31 weeks). Complete remission achieved in 65% (n = 80) (median duration 53.50 weeks), 23% (n = 28) experienced PR, SD was maintained in 3% (n = 4) and 4% (n = 5) experienced PD.

SS/MF

There are 91 patients over three phase I/phase II studies and four case reports (79 MF, 13 SS). All patients (n = 91) were CD30⁺ with variable expression. Sixty five percent (n = 58) experienced an OR (median duration 14.4 weeks). Complete remission was achieved in 17% (n = 13), 46% (n = 35) experienced a PR, SD was maintained in 5% (n = 4) and 7% (n = 5) experienced PD.

TCL

There are four phase I and one phase II study totaling 45 patients with PTCL. Of the available gender data, 67% (n = 28) were male (median age 58 years). All patients (n = 45) were CD30⁺ with variable expression. Of these, 48% (n = 22) experienced an OR (median duration 43.55 weeks). Complete remission was achieved in 35% (n = 15) (median duration 43.55 weeks), 16% (n = 7) experienced a PR, SD was maintained in 13% (n = 6) and 36% (n = 16) experienced PD.

LyP

There are nine total patients within one phase II study. All patients (n = 9) were CD30⁺. Of these, 100% (n = 9) achieved an OR (median duration 23 weeks). Complete remission was achieved by 56% (n = 5) and 44% (n = 4) experienced a PR.

pc-ALCL

There are six total patients over one phase II study and two case reports. All patients (n = 6) were CD30⁺. Of these, 100% (n = 6) experienced an OR (median duration 26 weeks) all of which were classified as CR (median duration 17 weeks).

PBL

There are two total patients over one phase II study and one case report. All patients (n = 2) were CD30⁺. An OR was experienced by 50% (n = 1) (median duration three days). A PR was experienced by 50% (n = 1) (median duration three days) and 50% (n = 1) experienced PD.

8. Discussion

The CD30 antibody is targeted by BV as an ADC comprising a CD30-directed antibody, conjugated to the microtubule-disrupting agent MMAE via a protease cleavable linker (Younes et al., 2012). CD30⁺ hematological malignancies in the relapsed and refractory setting have significantly worse outcomes compared to those with newly diagnosed disease. CD30 has been targeted with some success for relapsed hematological malignancies. CD30 can be expressed on the cell surface and in the cytoplasm but correlation between surface expression of CD30 and expression of cytoplasmic CD30 remains unclear (Blatt et al., 2015). CD30 targeting has shown to produce growth inhibition (G2/M cell cycle arrest) and apoptosis in neoplastic cells. The bystander effect and Fc portion mediated antibody dependent phagocytosis are also postulated as possible mechanisms for activity. CD30 expression is possibly regulated in many ways, one of which is the RAS-MEK-dependent pathway as described in MCs. Other proposed mechanisms include the nuclear factor- κ B (NF- κ B) pathway, MAPKs (i.e. extracellular-regulated kinase [ERK], Jun N-terminal kinase [JNK]) and p38 (Al-Shamkhani, 2004).

Understanding about laboratory methods to define and determine CD30 expression (cytoplasmic, serum and surface), its correlation with targeted drug therapy and clinical outcome is evolving. CD30 determination is commonly done by routine immunohistochemistry (IHC) staining using the antibody like anti-CD30 BerH2. CD30 positivity is defined as >1% surface expression on neoplastic cells. CD30 surface expression can be determined by computer-assisted methods using pixel-based image processing techniques. Soluble CD30 (sCD30) concentrations can be measured with commercial bead-based sandwich fluoroimmunoassay. Studies have shown that it is possible to have elevated sCD30 at baseline and quantifiable level of CD30 expression by computer-assisted methods, even if the visual assessment of IHC is negative for CD30 expression. Data reveal that there is a lack of clear correlation between the level of surface CD30 or sCD30 and response to BV. Many hypotheses are postulated to explain this discrepancy such as heterogeneous CD30 expression within the tumor with the possibility of a minimum threshold of CD30 required for clinical response (Jacobsen et al., 2015).

After excluding the data from studies in HL, we summarized data for NHLs and included results of phase I/II clinical trials (n = 14). Data from case reports (n = 14) was included due to the paucity of data on the subject and lack of randomized trials. There is no available phase III data on the subject. We stratify the study populations into three specific groups: B-cell malignancies (group A), T-cell malignancies (group B), and non-B or non-T-cell hematological malignancies (group C). We found clinical evidence for the efficacy of BV in twelve non-Hodgkin hematological malignancy subtypes.

Among B-cell lymphomas including DLBCL, FL, PMBL, PTL, and GZL studies, 51% (n = 44) of patients achieved an OR and 29% (n = 25) achieved CR with BV treatment. In a small study by Bartlett et al., it was observed that in DLBCL patients even with undetectable CD30 by traditional IHC staining, an OR was observed in 27% (n = 6) of patients. Only three patients were treated with advanced FL and two of these showed SD at best. Out of six patients with relapsed/refractory PMBL, three patients had SD and one CR was seen. Among less than ten PTL patients, almost half showed an OR (Bartlett et al., 2014b). Among patients with T-cell lymphomas with evidence of CD30 expression by IHC, 48% (n = 22) of these patients experienced an OR and 35% (n = 15) achieved CR. Additionally, ALCL patients showed objective responses in 87% of cases. Similarly, objective responses were noted in other subtypes such as LyP patients in which experience is limited (n = 9) but 100% positive responses were observed.

We recognize that limitations of this review are heterogeneity in disease subtypes and study design. Publication results are confounded by unmatched variable prognostic factors such as age, gender, prognostic score, molecular and genetic subtype, IPI score, grade and lymphoma stage, type, number of prior chemo- or immunotherapies, variable CD30 expression all of these are important factors to consider but have not been elaborated in many trials.

Further research, with appropriately powered prospective studies and strict diagnosis with clear identification of CD30 expression by IHC, sCD30 and computer assisted techniques along with other variables like prognostic factors, IPI score, grade, stage, prior therapies and outcome ascertainment, are needed to understand the BV efficacy in various CD30 positive malignancies. Ongoing studies with BV in CD30 positive hematological malignancies are summarized in Table 1. BV is being tested in various combinations with immunomodulatory agents such as lenalidomide, rituximab, single agent bendamustine and multi-agent chemotherapy, which may exhibit synergistic growth-inhibitory effects. Such combinations need to be tested based on pathologically active intracellular mechanism in each disease subtype. BV needs to be further studied in the setting of autologous and allogeneic HSCT for CD30⁺ malignancies to prevent post-HSCT relapse (Taverna et al., 2016; Gopal et al., 2012).

In conclusion, these studies have shown that the antibody-drug conjugate brentuximab vedotin induced positive responses in a variety of relapse and refractory NHL.

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GKB (co-first author): literature search, figures, study design, data collection, data analysis, data interpretation, writing, editing

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SL: literature search, figures, study design, data collection, data analysis, data interpretation

KR: literature search, figures, study design, data collection, data analysis, data interpretation

SY: data interpretation, writing, editing KG: literature search, figures, study design, data collection, data analysis, data interpretation

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AAS: literature search, study design, writing, editing

SP: data interpretation, writing, editing

FA (corresponding author): literature search, study design, data analysis, data interpretation, writing, editing

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Appendix 1. : Example Search Strategy

PubMed (1946–2015) Date searched: May 22, 2015

(((((“Hematologic Neoplasms” [Mesh:NoExp] OR “Lymphoma” [Mesh:NoExp] OR “Lymphoma, Non-Hodgkin” [Mesh] OR NHL [tw] OR (non [tw] AND hodgkin* [tw]) OR nonhodgkin* [tw] OR ((“b cell” [tw] OR “t cell” [tw] OR burkitt* [tw] OR “primary effusion” [tw] OR granulomatosis [tw] OR follicular [tw] OR immunoblastic [tw] OR lymphoblastic [tw] OR “mantle cell” [tw] OR anaplastic [tw] OR cutaneous* [tw] OR malt [tw] OR “mucosa associated lymphoid tissue” [tw] OR aggressive [tw] OR indolent [tw]) AND (lymphoma* [tw] OR malignan* [tw])) OR Dlbcl [tw] OR dlbl [tw] OR “papulosislymphomatoid” [tw] OR “mycosis fungoides” [tw] OR “pagetoidreticulosis” [tw] OR “sezary syndrome” [tw] OR ((cd30 [tw] OR cd30+ [tw] OR “cd 30” [tw] OR “cd 30+” [tw]) AND (lymphoma* [tw] OR malignan* OR neoplasm* [tw]))) AND (((“cAC10-vcMMAE” [Supplementary Concept] OR “Immunoconjugates” [Mesh:NoExp] OR Brentuximab [tw] OR Adcetris [tw] OR Anti-cd30 [tw] OR “Antibody drug conjugate” [tw] OR SGN-35 [tw] OR SGN35 [tw] OR cAC10-vcMMAE [tw]))) NOT (animals [mh] NOT humans [mh]))

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Fig. 1.

Trials selection process for the systematic review.

*Two additional studies included after initial screening

Table 1

Ongoing Clinical Trials.

Study	Pathology	Interventions	Outcomes
Phase I/II NCT01657331	HL, ALCL	BV+ Bendamustine	Safety and Efficacy
Phase II NCT02388490	Relapsed/refractory EBV and CD30 positive lymphomas	BV	ORR
Phase II NCT01393717	Relapse/refractory HL	BV prior to Auto SCT	Efficacy
Phase I/II NCT01805037	EBV and CD30 positive lymphomas	BV+ Rituximab as a first treatment	Safety and Efficacy
Phase I/II NCT02096042	AML	BV + 5-Azacytidine	Safety and Efficacy
Phase I/II NCT01771107	Stage II–IV HIV associated HL	BV + AVD	Safety and Efficacy
Phase II NCT02567851	HL	BV	Efficacy
Phase II NCT02423291	Relapse/refractory PMLBCL	BV	Safety and Efficacy
Phase I/II NCT01492088	Pediatric relapsed/refractory HL and ALCL	BV	Safety and Efficacy
Phase 0 NCT01900496	Relapsed/refractory HL	BV+ Rituximab	Efficacy
Phase I NCT02254239	Relapsed/refractory HL	BV+ Everolimus	Safety
Phase I/II NCT02462538	Relapsed/refractory ALK positive ALCL	BV+ Imatinib	Safety and Efficacy
Phase IV NCT01990534	Relapsed/refractory HL	BV	Efficacy
Phase II NCT02298257	Stage III–IV HIV associated HL	BV	Safety and Efficacy
Phase I NCT01896999	Relapsed/refractory HL	BV+ Ipilimumab/nivolumab	Safety and Efficacy
Phase II NCT02169505	High risk CD30 positive lymphoma	BV post allogeneic SCT	Safety and Efficacy
Phase I NCT02164006	HL	BV + PI3 K inhibitor (TGR-1202)	Safety and Efficacy
Phase I/II NCT02227199	Relapsed/refractory HL	BV + ICE	Safety and Efficacy
Phase III NCT01578499	CD30 positive cutaneous T-cell lymphoma	BV vs. Physician's choice (methotrexate or bexarotene)	Efficacy
Phase II NCT01979536	Stage II–IV ALCL	BV vs. Crizotinib in combination with chemotherapy as a first treatment	Safety and Efficacy
Phase I NCT01979536	Relapse/refractory DLBCL	BV+ Lenalidomide	Safety
Phase II NCT01925612	DLBCL	BV + RCHOP or RCHP	Safety and Efficacy
Phase II NCT01716806	Newly diagnosed HL in adults age 60 and above	BV single agent BV + Dacarbazine BV + Bendamustine	Efficacy
Phase II NCT02588651	Relapsed/refractory CD30 low (< 10%) mature T-cell lymphoma	BV	Efficacy

Study	Pathology	Interventions	Outcomes
Phase I/II NCT01874054	HL	BV + Bendamustine	Safety and Efficacy
Phase II NCT02280785	Relapsed/refractory CD30 positive NHL other than ALCL	BV	Efficacy
Phase II NCT02505269	Non-bulky limited stage HL	BV + Adriamycin + Dacarbazine	Efficacy
Phase I/II NCT02429375	Relapsed/refractory HL	BV + Mocetinostat (MGCD0103)	Safety and Efficacy
Phase I/II NCT02581631	NHL	BV + Nivolumab	Safety and Efficacy
Phase III NCT02684292	Relapsed/refractory HL	BV vs. Pembrolizumab	Safety and Efficacy
Phase IV NCT01909934	Relapsed/refractory systemic ALCL	BV	Safety and Efficacy
Phase I/II NCT02572167	Relapsed/refractory HL	BV + Nivolumab	Safety and Efficacy
Phase II NCT02227433	First relapse or primary refractory elderly HL	BV	Efficacy
Phase II NCT02594163	CD30 positive DLBCL	Rituximab and Bendamustine ± BV	Safety and Efficacy
Phase I NCT01309789	CD30 positive mature T-cell and NK neoplasms	BV + Chemotherapy	Safety
Phase II NCT02497131	Relapsed/refractory CD30 positive PTCL	BV	Safety and Efficacy
Phase II NCT02623920	Relapsed/refractory B-cell NHL	BV + Rituximab + Bendamustine	Efficacy
Phase II NCT02275598	Previously untreated HL	BV followed by AVBD	Safety and Efficacy
Phase II NCT02191930	Older patients with newly diagnosed HL	BV + CAP	Safety and Efficacy
Phase I NCT02616965	Cutaneous T-cell lymphoma	BV + Romidepsin	Safety and Efficacy
Phase II NCT02292979	Untreated HL	BV + ABVD	Safety and Efficacy
Phase I/II NCT01994850	CD30 positive PMLBCL, DLBCL, GZL	BV + Chemotherapy	Safety and Efficacy
Phase II NCT01476410	Older patient with previously untreated Stage II–IV HL	BV + Chemotherapy	Efficacy
Phase II NCT01352520	CD30 positive ALCL, MF, LyP	BV	Safety and Efficacy

Abbreviation: HL (Hodgkin lymphoma), NHL (non-Hodgkin lymphoma), Primary mediastinal large B-cell lymphoma (PMLBCL), ALCL (anaplastic large cell lymphoma), DLBCL (diffuse large B-cell lymphoma), GZL (gray zone lymphoma), MF (mycosis fungoides), LyP (lymphomatoid papulosis), BV (brentuximab vedotin), ICE (ifosfamide + carboplatin + etoposide), RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), RCHP (rituximab, cyclophosphamide, doxorubicin, and prednisone), CAP (cyclophosphamide, doxorubicin, prednisone).