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CCR Drug Updates

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Brentuximab Vedotin

Changchun Deng[1], Beiqing Pan[2], and Owen A. O'Connor[1]

Abstract

Brentuximab vedotin (SGN-35), an intravenously administered CD30-specific antibody–drug conjugate, has recently been approved by the U.S. Food and Drug Administration for two indications, including (i) patients with Hodgkin lymphoma relapsing after autologous stem-cell transplantation (ASCT), or after two multidrug regimens in patients with Hodgkin lymphoma who are not candidates for ASCT; and (ii) patients with systemic anaplastic large cell lymphoma (ALCL) who failed at least one prior multidrug chemotherapy regimen. Patients with Hodgkin lymphoma and ALCL treated with brentuximab vedotin showed markedly high response rates for a single agent, exceeding 70% and 80% for Hodgkin lymphoma and ALCL, respectively. The complete response rate was equally as impressive, at 34% and 57% for Hodgkin lymphoma and ALCL, respectively. Results like these and from many other upcoming clinical trials, in which brentuximab vedotin is being investigated in the frontline setting, promise to profoundly change how we manage the CD30-positive lymphoproliferative malignancies. The mechanism of action, preclinical antitumor activity, and clinical activity of brentuximab vedotin against Hodgkin lymphoma, ALCL, and other CD30-expressing lymphomas are reviewed. *Clin Cancer Res; 19(1); 22–27. ©2012 AACR.*

Introduction

In August 2011, the U.S. Food and Drug Administration (FDA) approved brentuximab vedotin, or SGN-35 (Adcetris; Seattle Genetics), a CD30-specific antibody–drug conjugate, for the treatment of patients with Hodgkin lymphoma relapsing after autologous stem-cell transplantation (ASCT), or after 2 multidrug regimens in patients with Hodgkin lymphoma who are not the candidates for ASCT. Brentuximab vedotin was also approved for patients with systemic anaplastic large cell lymphoma (ALCL) who failed at least one prior multidrug chemotherapy regimen (1).

Hodgkin lymphoma is a rare cancer with estimated 9,060 new cases annually in the United States (2), and is considered highly curable with long-term survival rates exceeding 80% (3). However, approximately 5% of early-stage disease and 30% to 40% of advanced stage disease relapse after first-line treatment. Patients with relapsed and refractory Hodgkin lymphoma typically receive salvage chemotherapy followed by ASCT (4). However, for patients who relapse after ASCT, effective therapeutic options are limited. ALCL is a T-cell non-Hodgkin lymphoma (NHL) that accounts for less than 5% of adult lymphomas and 40% of pediatric NHL (5). ALCL is further classified into 2 distinct subtypes based on the expression of anaplastic lymphoma kinase (ALK). Patients with the t(2;5) translocation are characterized by lymphoma cells expressing the ALK, and exhibit a 5-year overall survival rate of 70%, compared with 49% for those patients with ALK-negative ALCL (5). Monoclonal antibody therapy directed against unique antigens expressed on cancer cells has been successfully integrated into many treatment paradigms. Antibody–drug conjugates (ADC) represent an extension of this technology and allow delivery of high doses of cytotoxic drugs to cancer cells, largely sparing normal tissues (6). Brentuximab vedotin, a CD30-directed monoclonal antibody conjugated to the potent inhibitor of microtubule polymerization monomethyl auristatin E (MMAE), is highly effective in selectively targeting and killing CD30-expressing lymphoma cells.

Preclinical data

CD30 was originally discovered in 1982 by Schwab and Diehl using a monoclonal antibody, Ki-1, that recognized a molecule selectively and was highly expressed by Reed–Sternberg cells in Hodgkin lymphoma (7). CD30 is also highly and uniformly expressed on the surface of ALCL cells and at variable levels in many other subtypes of NHL (8, 9). CD30 expression is typically not detectable on healthy tissues outside the immune system or on resting lymphocytes and monocytes, but is expressed in the medullary of the thymus gland and a subset of activated T cells (both CD4+ and CD8+) and B cells (10). A soluble form of CD30 has been found to be elevated in the serum of patients with

Authors' Affiliations: [1]Center for Lymphoid Malignancies and [2]Division of Medical Oncology, Columbia University Medical Center, New York, New York

Corresponding Authors: Changchun Deng, Center for Lymphoid Malignancies, Columbia Univeristy, 16 East 60th Street, Suite 330, New York, NY 10022. Phone: 212-326-5720; Fax: 212-326-5725; E-mail: cd2448@mail.cumc.columbia.edu; and Owen A. O'Connor, E-mail: oo2130@columbia.edu

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Hodgkin lymphoma and other CD30-expressing tumors, as well as in inflammatory conditions characterized by strong T- or B-cell activation. The high levels of expression on specific cancers and limited expression on healthy tissues make CD30 an attractive target for antibody-based immunotherapy.

CD30 is membrane glycoprotein that belongs to the TNF receptor (TNFR) superfamily (11), which comprises 29 members, including Fas and TNFR1 (12). The interaction of TNFRs and their ligands is transduced through the recruitment of a variety of adaptor proteins, including TNFR-associated factor 2 (TRAF2). TNFR signaling activates the IκB kinase 2 (IKK2) and the NF-κB pathway, thereby promoting cellular proliferation and survival; however, it can also activate apoptosis in some experimental models (12). The CD30 signaling pathway has been carefully studied *in vitro*, and is found to be intricately linked to NF-κB. For example, using a chimeric protein CD28–CD30 that initiated CD30 signal transduction in a ligand-independent manner, Duckett and colleagues showed that stimulation of CD30 signaling indirectly inhibited the activation of NF-κB in the human embryonic kidney cell line 293, by causing degradation of TRAF2, thereby preventing its recruitment of a protein complex that is required to effectively activate IKK2 (13). Similarly, a CD30 agonistic antibody, M67, has been shown to inhibit the activation of NF-κB in ALCL cells, thereby inducing apoptosis of ALCL cells (14). Endogenous CD30 ligand (CD30L) is absent in ALCL cells, and activation of CD30 signaling using exogenous CD30L results in inhibition of ALCL cell lines (15). In contrast, Hodgkin lymphoma cells are resistant to CD30-mediated apoptosis, as these cells have constitutively activated NF-κB that is not subject to inhibition by CD30 signaling. Indeed, activation of CD30 signaling using the exogenous CD30L results in proliferation of Hodgkin lymphoma cells (15). Interestingly, endogenous CD30L is present in the cytoplasm of Reed–Sternberg cells on tissue sections from patients with Hodgkin lymphoma, suggesting that a CD30L–CD30 autocrine loop may contribute to the different pathogenesis between Hodgkin lymphoma and ALCL. The relevance of CD30 in lymphoma pathogenesis remains poorly understood, and the CD30 signaling pathway itself has not been a promising drug target. Research efforts have been directed mainly toward immunotherapies that exploit the highly selective expression of CD30 in lymphoma cells.

SGN-30 (also known as cAC10), a chimeric anti-CD30 monoclonal antibody, is constructed from the variable regions of the anti-CD30 murine monoclonal AC10 and the constant regions of human gamma 1 heavy chain and kappa light chain, and recognizes a unique CD30 epitope different from other anti-CD30 antibodies (16). Studies in Hodgkin lymphoma cell lines and xenograft mouse models have shown the antitumor activity of SGN-30 in Hodgkin lymphoma, presumably through antibody-dependent cell-mediated cytotoxicity (ADCC; refs. 17, 18). However, although SGN-30 has shown anticancer activity in preclinical studies, its activity in phase II clinical trials was disappointing (19). Of 41 patients with ALCL, 5 achieved partial response and 2 achieved complete response, including one with the duration of response exceeding 1,460 days. In contrast, no responses were seen in 38 patients with Hodgkin lymphoma. The dichotomy of response by these 2 types of CD30-positive lymphoma to the naked CD30 antibody, although lacking statistical significance, is interesting, as it may be predicted from the *in vitro* results discussed above, which show that CD30 signaling inhibits the growth and survival of ALCL cells, but causes proliferation in Hodgkin lymphoma cells. The minimal clinical activity of unconjugated anti-CD30 antibodies helped to shift the research focus from ADCC to alternative strategies that attack the tumor cells directly and selectively, including ADCs. ADCs allow delivery of drugs that are excessively toxic if not conjugated to monoclonal antibodies.

Brentuximab vedotin, or SGN-35, is generated by conjugating SGN-30 to the synthetic antitubulin agent MMAE, an analogue of the marine natural product dolastatin 10, through an enzyme-cleavable valine–citrulline dipeptide (20). Brentuximab vedotin binds to the extracellular domain of CD30, becomes internalized by clathrin-mediated endocytosis, and subsequently travels to the lysosome where proteases cleave the linker peptide and release MMAE into the cytosol (21). MMAE binds to tubulin and potently inhibits microtubule polymerization, inducing G_2–M phase growth arrest and apoptosis in CD30-expressing lymphoma cells (Fig. 1). MMAE is also diffusible from the CD30-positive lymphoma cells into their surrounding microenvironment, where it may exert a bystander effect as an important, possibly essential mechanism of killing lymphoma cells. This concept has been suggested by the sometimes low occupancy of CD30-binding sites, as low as 3%, in lymphoma cells from highly responsive patients treated with brentuximab vedotin (22). Administration of brentuximab vedotin to mice carrying Hodgkin lymphoma and ALCL tumors induced regressions and cures of established tumor xenografts with excellent therapeutic indices (23, 24). In addition, the combination of brentuximab vedotin with chemotherapeutic drugs exhibited synergistic antitumor activity in preclinical models of Hodgkin lymphoma (25). Brentuximab vedotin has proven to be a highly promising drug for patients with CD30-positive lymphoma.

Clinical Studies

Safety and tolerability

Younes and colleagues initiated a phase I clinical trial in 2006 to evaluate brentuximab vedotin for patients with CD30-positive lymphomas, the majority of which were relapsed Hodgkin lymphoma (26). Brentuximab vedotin was administered at doses of 0.1 to 3.6 mg/kg of body weight every 3 weeks for a 3-week cycle, using a traditional dose-escalation design. A single patient, who received 3.6 mg/kg of the drug, developed febrile neutropenia and later succumbed to sepsis. Dose-limiting toxicity occurred in 1 of 6 patients receiving either 1.8 mg/kg or 2.7 mg/kg of

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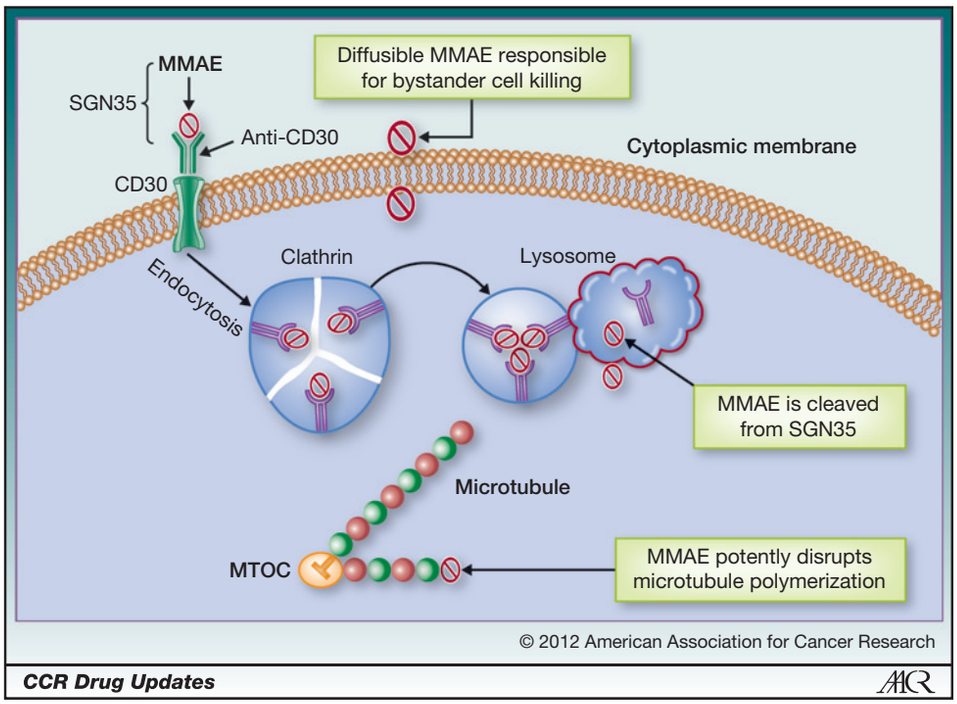

Figure 1. Mechanism of action of brentuximab vedotin. Each molecule of brentuximab vedotin (SGN-35) is conjugated with 4 molecules of MMAE. Upon binding of SGN-35 to its receptor, CD30, the complex undergoes clathrin-mediated endocytosis. The endosome subsequently fuses with lysosomes, where the proteases cleaved the dipeptide linker in SGN-35, releasing free MMAE into the cytoplasm. MMAE inhibits microtubule polymerization and causes cell death. MMAE may be diffused out of the cytoplasm, where it may enter and kill surrounding cells, so-called "bystander" effect, independently of whether CD30 is expressed. MTOC, microtubule organizing center.

the drug. Enrollment to these 2 dose cohorts was expanded to a total of 12 patients in each cohort. The cohort receiving 2.7 mg/kg of the drug was found to have several dose-limiting toxicities, including grade 4 thrombocytopenia, grade 3 hyperglycemia, and grade 3 unrelated prostatitis and febrile neutropenia, and was considered to have unacceptable toxic effects. The dose of 1.8 mg/kg of body weight, given intravenously once every 3 weeks, was determined to be the maximum tolerated dose (MTD). Brentuximab vedotin was generally well tolerated, with the most common adverse events (AE) reported in this trial being fatigue, pyrexia, diarrhea, nausea, neutropenia, and peripheral neuropathy. Fanale and colleagues investigated the safety of weekly brentuximab vedotin in primarily relapsed patients with Hodgkin lymphoma (27). The MTD was determined to be 1.2 mg/kg given weekly for 3 weeks in a 4-week cycle. The toxicities seen on the weekly administration were similar to those on the once every 3-week schedule, but occurred more frequently. Subsequent phase II trials adopted the schedule of brentuximab vedotin administered once every 3 weeks.

A pivotal phase II clinical trial was conducted by Younes and colleagues, who treated 102 patients with relapsed Hodgkin lymphoma after ASCT with brentuximab vedotin, administered intravenously at 1.8 mg/kg of body weight once every 3 weeks (28). Patients tolerated the treatment very well, receiving a median number of 9 cycles, with only 8% of doses delayed because of AEs. The most common treatment-related AEs, in descending orders of frequency, included peripheral neuropathy (42%), nausea, fatigue, neutropenia, diarrhea, pyrexia, vomiting, arthralgia, pruritus, myalgia, peripheral motor neuropathy, and alopecia (10%). Grade 3 or higher toxicities were mainly hematologic, including neutropenia (20%), thrombocytopenia (8%), and anemia (6%). The only significant nonhematologic toxicity of grade 3 or higher was peripheral sensory neuropathy (8%), which was the reason for treatment discontinuation in 9 of 20 patients, and the reason for dose reduction in 10 of 11 patients. Peripheral neuropathy was potentially reversible, with complete resolution of peripheral neuropathy occurring in 50% of the affected patients. The median time to symptom improvement or resolution was 13.2 weeks. Another phase II clinical trial was conducted by Pro and colleagues, who evaluated brentuximab vedotin administered at 1.8 mg/kg once every 3 weeks for relapsed or refractory systemic ALCL (29). They reported very similar toxicities to those reported by Younes and colleagues, as well as some additional AEs, including constipation (22%), headache (19%), cough (17%), dyspnea (17%), decreased appetite, insomnia, and weight loss, all of which were grade 1 or 2. When combined with a bleomycin-containing regimen, brentuximab was associated with increased pulmonary toxicity (30). As a result, a boxed warning of pulmonary toxicity has been added by the FDA to brentuximab. Another boxed warning for brentuximab is for rare (total of 3 cases so far) progressive multifocal leukoencephalopathy.

Efficacy in Hodgkin lymphoma

In the initial phase I study that included mostly relapsed patients with Hodgkin lymphoma (26), 17 of 45 enrolled patients experienced an objective response, defined as either complete response (CR) or partial response (PR) based on the 2007 Revised Response Criteria for Malignant

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Table 1. Efficacy of brentuximab vedotin in phase II studies

Lymphoma type (ref.)	Disease control (%)	ORR (%)	CR (%)	PR (%)	DOR-all (mon)	DOR-CR (mon)
Hodgkin lymphoma (28)	99[a]	75	34	41	6.7	20.5
ALCL (29)	97[b]	86	57	29	12.6	13.2

Abbreviations: DOR-all, duration of response for all patients; DOR-CR, duration of response for patients who achieved CR.
[a]Refers to the frequency of patients who achieved CR, PR, or stabilization of their tumors.
[b]Refers to the frequency of patients who achieved reduction of their tumors.

Lymphoma (31). Patients with an objective response, almost all, received brentuximab vedotin at doses of 1.2 mg/kg or higher. In the pivotal phase II study of relapsed Hodgkin lymphoma, in which brentuximab vedotin was given at the MTD dose of 1.8 mg/kg every 3 weeks (28), after a median follow-up of 18.5 months, 99% of the patients achieved overall disease control, defined as either CR, PR, or stable disease (Table 1). The primary end point objective response rate (ORR), was 75%. The rates of CR and PR were 34% and 41%, respectively. Response was achieved relatively fast, with the median time to CR and PR being 12 and 5.7 weeks, respectively. Importantly, patients achieving CR had a much longer duration of response, over 20 months, compared with 6.7 months for all patients with objective response (CR + PR). Similarly, the median progression-free survival (PFS) was notably longer for patients who achieved CR than those achieving PR, at 21.7 and 5.2 months, respectively.

Efficacy in ALCL

Pro and colleagues recently reported the results of a phase II study of brentuximab vedotin in relapsed or refractory systemic ALCL (29), summarized in Table 1. A total of 58 patients were enrolled and received the drug at the MTD of 1.8 mg/kg once every 3 weeks. Tumor reduction was observed in 97% of the patients. The primary end point of ORR was 86%, with 57% of patients achieving CR, and 29% PR. Again, responses were attained relatively fast, with the median time to objective response and CR being 5.7 and 11.9 weeks, respectively. The median duration of response for all patients was 12.6 months, compared with 13.2 months for those achieving CR. Importantly, both ALK-positive and ALK-negative patients with ALCL treated with brentuximab vedotin achieved comparable and high response rates.

Efficacy in other settings

Preliminary results from a phase II clinical trial have shown the efficacy of brentuximab vedotin in other subtypes of NHL that have various levels of CD30-positive cells, including diffuse large B-cell lymphoma (DLBCL), EBV-positive DLBCL of the elderly, primary mediastinal B-cell lymphoma, peripheral T-cell lymphoma, and angioimmunoblastic T-cell lymphoma (AITL; ref. 32). Of 6 evaluable patients, 2 achieved CR, including 1 with DLBCL (CD30-positive cells: 90%) and 1 with AITL (CD30-positive cells: 8%). Retreatment with brentuximab vedotin after relapse is also possible, as suggested by the preliminary results of a phase II trial (33). Objective responses were observed in 13 of 20 patients previously treated with brentuximab vedotin. At present, it remains unknown whether a threshold of the percentage of CD30-positive lymphoma cells exists that is required for brentuximab vedotin to be effective. In the previously mentioned phase II clinical trials, the tissue expression level and distribution pattern of CD30 in human Hodgkin lymphoma and ALCL were not discussed in detail.

Comparison with other agents

As a single agent for relapsed Hodgkin lymphoma and ALCL, brentuximab vedotin has clearly produced highly favorable treatment responses, at least in terms of ORR, rates of CR and PR, and duration of response. Furthermore, brentuximab vedotin is well tolerated. The dose-limiting nonhematologic toxicity is peripheral neuropathy, which is potentially reversible. The efficacy of brentuximab vedotin also stands out among other ADCs in clinical development, including trastuzumab-DM1 and inotuzumab ozogamicin, which reported ORR below 40% in patients with breast cancer and lymphoma, respectively. While the mechanism underlying the superior efficacy of brentuximab vedotin as an ADC is not fully understood, it is being intensely studied to expand the next generation of ADCs for the treatment of lymphoma.

Conclusions and challenges

Brentuximab vedotin is a first-in-class antibody–drug conjugate approved by the FDA. Its impressive efficacy and favorable toxicity profile promise to bring exciting opportunities for more drugs in this class that can selectively target and potently kill cancer cells. With its recent approval, brentuximab vedotin will likely impact the long-term outcomes of many of patients who have relapsed Hodgkin lymphoma or ALCL, by creating new windows of opportunity for ASCT and allogeneic stem-cell transplant. Brentuximab vedotin is currently in a number of clinical trials where it is being combined with chemotherapeutic drugs, including in the upfront setting of Hodgkin lymphoma. However, neurotoxicity may be a significant barrier to the combination of brentuximab vedotin with other neurotoxic drugs like the vinca alkaloids. Furthermore, as current frontline regimens for Hodgkin lymphoma are already

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producing very good survival, it may be difficult to reach the statistical power to show any added survival benefit attributable to brentuximab vedotin in the upfront setting. The bystander effect caused by diffusible MMAE has been suggested to be an important mechanism of brentuximab vedotin. It remains unknown how much and how far free MMAE may be diffusible in different lymphomas. These answers may provide important clues as to whether lymphomas with only a small percentage of CD30-positive lymphoma cells may still benefit from brentuximab vedotin. It is anticipated that careful preclinical work in this area, as well as novel clinical trials, will eventually provide the necessary guidance to treat patients with lymphomas other than Hodgkin lymphoma and ALCL using brentuximab vedotin. Interestingly, CD30 was found to be expressed on more than 2% of solid tumors (34), potentially representing more than 40,000 new cancer patients every year in the United States alone. A tantalizing and important question is whether these patients will respond to brentuximab vedotin as well as those with Hodgkin lymphoma or ALCL. If proven, the ultimate strategy of targeting discrete molecular markers of a disease, rather than the histologic subtypes, will be one large step closer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: C. Deng, O.A. O'Connor
Development of methodology: C. Deng, O.A. O'Connor
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C. Deng
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C. Deng, O.A. O'Connor
Writing, review, and/or revision of the manuscript: C. Deng, B. Pan, O.A. O'Connor
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C. Deng, O.A. O'Connor
Study supervision: C. Deng, O.A. O'Connor

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