Brentuximab Vedotin: A New Age in the Treatment of Hodgkin Lymphoma and Anaplastic Large Cell Lymphoma

Stephanie S Minich

OBJECTIVE: To review the clinical trial data, pharmacology, pharmacokinetics, and adverse effects of brentuximab vedotin.

DATA SOURCES: A literature search was performed using MEDLINE and PubMed (both 1966-October 2011), as well as the American Society of Hematology abstracts (2000-January 2012), using the primary search terms brentuximab vedotin, SGN-35, Hodgkin lymphoma (HL), and anaplastic large cell lymphoma (ALCL).

STUDY SELECTION AND DATA EXTRACTION: Published and ongoing clinical studies and abstracts in the English language that detail the pharmacology, pharmacokinetics, safety, and clinical efficacy of brentuximab vedotin in the treatment of HL and ALCL were included in this review.

DATA SYNTHESIS: Brentuximab vedotin is an antibody drug conjugate that combines the anti-CD30 antibody, cAC10, with the synthetic tubulin disrupting agent monomethyl auristatin E. A Phase 1 trial in patients with relapsed and refractory HL or systemic ALCL supported a dose of 1.8 mg/kg every 3 weeks. The drug was well tolerated, with the majority of adverse reactions being grade 1 or 2 in severity. Common toxicities included fatigue, pyrexia, diarrhea, nausea, neutropenia, and peripheral neuropathy. Phase 2 studies in the same patient populations illustrated objective response rates of 73-86% with an acceptable toxicity profile. Based on results of these Phase 2 trials, the Food and Drug Administration granted approval of brentuximab vedotin in August 2011 for the treatment of relapsed and refractory HL or ALCL.

CONCLUSIONS: Phase 1 and 2 clinical trial data indicate that brentuximab vedotin is efficacious and safe in patients with relapsed and refractory CD30-positive lymphomas. This agent is being investigated in combination with chemotherapy to further elucidate its role in lymphoma therapy.

KEY WORDS: anaplastic large cell lymphoma, brentuximab vedotin, Hodgkin lymphoma, SGN-35.

Ann Pharmacother 2012;46:377-83.

Published Online, 6 Mar 2012, *theannals.com*, DOI 10.1345/aph.1Q680

Hodgkin lymphoma (HL) is an uncommon, yet highly curable malignancy. Improvements in front-line therapy have resulted in an 80% cure rate.[1] In patients with relapsed or refractory HL, high-dose chemotherapy followed by autologous stem cell transplant (ASCT) is an option for a potential cure after failure of initial chemotherapy regimens.[2] However, ASCT may be effective in only 50% of patients.[2-4] Overall survival in patients who relapse post ASCT is 55% at 2 years and 32% at 5 years.[5] Patients who fail ASCT may be offered palliative chemotherapy, reduced-intensity allogeneic stem cell transplant, or involvement in a clinical trial.[6] Palliative chemotherapy with single-agent vinorelbine or gemcitabine has demonstrated efficacy in the relapsed/refractory scenario, but may produce excessive hematologic toxicity, and response durations are often short.[6] Allogeneic stem cell transplant may result in high morbidity and mortality, particularly in the elderly patient population.[6] Clearly, new therapies are necessary to improve survival rates in the setting of relapsed/refractory HL.

Anaplastic large cell lymphoma (ALCL) is a T-cell non-Hodgkin lymphoma (NHL), which may present as local cutaneous or aggressive systemic disease.[7,8] Systemic ALCL is classified as anaplastic lymphoma kinase (ALK) positive or negative, with 60% of cases being ALK positive.[7] ALK-positive ALCL confers a better survival rate than does ALK-negative disease; Savage et al. reported a 5-year overall survival rate of 93% in patients with ALK-positive disease compared with 37% in ALK-negative disease.[9] ALK-positive ALCL responds well to front-line chemotherapy, and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) therapy is a regimen frequently used.[7] However, patients with relapsed or refractory ALK-negative ALCL have a 5-year, progression-free survival rate of

Author information provided at end of text.

less than 25% post ASCT.[10] Currently, there is no standard of care for patients with ALCL who relapse after ASCT. Novel treatment options are necessary to improve response and overall survival rates for ALCL, particularly in ALK-negative disease.

Immunotherapy is an alluring option for treatment of many malignancies, as it offers targeted therapy against specific antigens with ideally decreased systemic toxicity. Multiple immunotargets have been identified and investigated in the treatment of HL and other lymphomas.[11-15] The CD30 antigen, a member of the tumor necrosis factor receptor family, is expressed on the surface of Hodgkin Reed-Sternberg (HRS) and ALCL cells. While CD30 is highly expressed in HRS and ALCL cells, its expression is quite restricted in healthy individuals.[11-15] Thus, CD30 is a prime target for antibody-based therapy in the treatment of these malignancies. In fact, several anti-CD30 agents have been studied. The first-generation antibodies SGN-30 (cAC10) and MDX-060 showed acceptable toxicity profiles but limited overall response rates in patients with CD30-positive malignancies.[12,13] The second-generation antibody XmAb2513 (humanized cAC10) is being investigated in a Phase 1 study in the same patient population; the drug appears to be well tolerated but its clinical efficacy is not fully known.[12] Given the lack of clinical success with unconjugated anti-CD30 antibodies, antibody drug conjugates (ADCs) have been explored to improve antitumor response.

Brentuximab vedotin is a novel ADC approved by the Food and Drug Administration (FDA) in August 2011 for the treatment of relapsed and refractory HL (after ASCT failure or failure of at least 2 prior chemotherapy regimens) and systemic ALCL (after failure of at least 1 prior chemotherapy regimen). This article reviews the clinical trial evidence supporting its approval, as well as discusses the properties of the drug, such as mechanism of action, pharmacokinetics and pharmacodynamics, and adverse events.

Data Sources and Selection

A literature search was performed, using MEDLINE and PubMed (both 1966-October 2011) as well as the American Society of Hematology abstracts (2000-January 2012), for English-language articles, using the primary search terms brentuximab vedotin, SGN-35, HL, and ALCL. Published reports and ongoing Phase 1-3 clinical trials evaluating the safety and efficacy of brentuximab vedotin were reviewed. Prescribing information and data on file from the manufacturer were used to supplement information from the clinical trials.

Mechanism of Action

Brentuximab vedotin is an ADC that combines the chimeric anti-CD30 antibody cAC10 with the synthetic tubulin-disrupting agent monomethyl auristatin E (MMAE).[11-15] Each antibody is conjugated to 4 molecules of MMAE via a dipeptide linker. Upon binding to CD-30 receptor positive malignant cells, the ADC is internalized by endocytosis. Lysosomal degradation causes selective cleavage of the linker, thus allowing the MMAE to be released. The MMAE molecules bind to tubulin, effectively disrupting the microtubule network with resultant cell cycle arrest and apoptosis.[11-15] MMAE may have a direct killing result not only on the CD30-expressing cell, but also on surrounding cells by diffusion from the cell into surrounding stroma. This proposed mechanism is beneficial in allowing cells in the tumor cell vicinity that did not properly internalize the ADC to be destroyed.[13]

Pharmacodynamics and Pharmacokinetics

Phase 1 data indicate that maximum concentration of the ADC occurs close to the end of the infusion, while that of the MMAE happens approximately 1-3 days postinfusion. Increasing exposure to the ADC and unbound MMAE were approximately dose proportional. With every 3-week dosing, steady-state concentrations of the ADC and MMAE occurred within 21 days. Terminal half-life of the ADC and MMAE is estimated to be 4-6 days and 3-4 days, respectively.[2]

In vitro data illustrate that MMAE has a 68-82% human plasma protein binding incidence and is not likely to either displace or be affected by highly protein-bound drugs. MMAE is a P-glycoprotein (P-gp) substrate, but is not a potent P-gp inhibitor. Human studies have shown the mean steady-state volume of distribution to be approximately 6-10 L. MMAE metabolism occurs primarily through CYP3A oxidation; however, only a small proportion of unbound MMAE is metabolized. At the clinical dose of 1.8 mg/kg, neither MMAE nor brentuximab vedotin appears to be an inhibitor or inducer of CYP3A4.[16]

The elimination of MMAE is limited by its rate of release from the ADC. In patients who received brentuximab vedotin 1.8 mg/kg, about 24% of the total MMAE was recovered in both urine and feces over a 1-week period. The majority (72%) of the recovered MMAE was found in the feces and was unchanged.[17]

Clinical Studies

The designs and results of brentuximab vedotin clinical trials in the setting of relapsed and refractory HL and ALCL are described in Table 1; adverse events experienced during Phase 2 trials are summarized in Table 2. Brentuximab vedotin was evaluated in a Phase 1 weekly dosing study in patients with relapsed or refractory CD30-positive lymphomas.[18] The drug was administered weekly for 3 weeks in 28-day cycles at doses of 0.4-1.4 mg/kg. A

total of 44 patients with Hodgkin lymphoma, ALCL, or peripheral T-cell lymphoma were enrolled. Patients had received anywhere from 1 to 8 prior chemotherapy regimens, and 68% had undergone ASCT. More than 50% of study participants had not responded to their most recent therapy. Common adverse effects were peripheral sensory neuropathy (66%), nausea (50%), fatigue (52%), diarrhea (32%), and pyrexia (25%); most reactions were grade 1 or 2 in severity. Grade 3 toxicities included peripheral sensory neuropathy (14%); anemia (9%); neutropenia (7%); and hyperglycemia, diarrhea, and vomiting (5% each). Grade 4 toxicities were hyperglycemia and neutropenia (seen in 1 patient each). Patients were not routinely premedicated prior to brentuximab vedotin infusion; mild-to-moderate infusion-related reactions were seen in 6 (14%) patients. The objective response rate (ORR) was 59% (24 of 41 evaluable patients), with 34% of patients achieving complete remission. The median duration of response was not reached at a median follow-up of 45 weeks. Weekly brentuximab vedotin provided a high rate of objective response in relapsed and refractory CD30-positive malignancies, with acceptable toxicity.[18]

Another Phase 1, open-label, dose-escalation study evaluated the safety and maximum tolerated brentuximab vedotin dose when given on an every-3-week schedule; secondary objectives included pharmacokinetic analysis, immunogenicity, and antitumor response.[2] Like the previously described study, eligible patients had relapsed or refractory CD30-positive hematologic cancers. Brentuximab vedotin was administered at doses of 0.1-3.6 mg/kg every 3 weeks, following a traditional dose-escalation design. Forty-five patients received treatment and had previously undergone a median of 3 chemotherapy regimens; 33 patients (73%) had received an autologous bone marrow transplant.

The dose-escalation phase revealed a dose-limiting toxic effect of grade 4 thrombocytopenia in 1 of 6 patients who received 1.8 mg/kg/dose. Grade 3 renal failure occurred in 1 of 6 patients who received 2.7 mg/kg. In addition, grade 3 hyperglycemia (1 patient) and grade 3 prostatitis and febrile neutropenia (1 patient) were observed at this dose. Only 1 patient received 3.6 mg/kg and subsequently experienced febrile neutropenia and presumed sepsis. Thus, 1.8 mg/kg was determined to be the maximum tolerated dose.[2]

Brentuximab vedotin was well tolerated, with the majority of adverse reactions being grade 1 or 2 in severity. Common adverse effects included fatigue (36%); pyrexia (33%); and diarrhea, nausea, neutropenia, and peripheral neuropathy (22% each). Dose delays due to fatigue and thrombocytopenia occurred in 2 patients each (4%). One patient discontinued therapy after an anaphylactic reaction

Table 1. Brentuximab Vedotin Clinical Trials

Reference	Design	Treatment	Efficacy Results	Safety Results
Fanale (2011)[18]	Phase 1, MC, dose-finding N = 44 (38 HL, 5 ALCL, 1 PTCL)	Brentuximab vedotin 0.4-1.4 mg/kg/dose weekly for 3 wk every 28 days (30-minute or 2-hour iv infusion)	ORR: 59% (24/41) CR: 34% (14/41)	MTD: 1.2 mg/kg/dose Common AEs: peripheral neuropathy, nausea, fatigue, diarrhea, dizziness, neutropenia (most grade 1/2) Grade 3: peripheral sensory and motor neuropathy, anemia, neutropenia Grade 4 (1 pt. each): hyperglycemia, neutropenia
Younes (2010)[2]	Phase 1, MC, OL, dose-escalating, cohort expansion N = 45 (42 HL, 2 ALCL, 1 angioimmunoblastic T-cell lymphoma)	Brentuximab vedotin 0.1-3.6 mg/kg/dose every 3 weeks <1.2 mg/kg (n = 16) 1.2 mg/kg (n = 4) 1.8 mg/kg (n = 12) 2.7 mg/kg (n = 12) 3.6 mg/kg (n = 1)	ORR: 38% (17/5) CR (overall): 24% (11/45) CR (1.8 mg/kg/dose): 50% (6/12) Tumor regression: 86% (36/42 evaluable pts.)	MTD: 1.8 mg/kg/dose Common AEs (any dose): fatigue, pyrexia, diarrhea, nausea, neutropenia, peripheral neuropathy, headache, constipation, arthralgia
Chen (2010)[19]	Phase 2, single-arm, MC N = 102 relapsed or refractory HL post ASCT	Brentuximab vedotin 1.8 mg/kg/dose iv every 3 weeks (30-minute infusion) up to 16 cycles	ORR: 73% CR: 32% PR: 40% B symptom resolution: 83%	Common AEs (any grade): peripheral sensory neuropathy, fatigue, nausea, neutropenia, diarrhea, pyrexia Grade 3: neutropenia, peripheral sensory neuropathy, thrombocytopenia, fatigue
Shustov (2010)[20]	Phase 2, single-arm, MC N = 58 relapsed or refractory ALCL	Brentuximab vedotin 1.8 mg/kg/dose iv every 3 weeks (30-minute infusion) up to 16 cycles	ORR: 86% CR: 57% PR: 29% Tumor size reduction in 97% of pts. B symptom resolution: 90%	Common AEs (any grade): nausea, diarrhea, peripheral sensory neuropathy, pyrexia, dyspnea, fatigue, insomnia, neutropenia Grade 3/4: neutropenia, peripheral sensory neuropathy, diarrhea, anemia

AE = adverse event; ALCL = anaplastic large cell lymphoma; ASCT = autologous stem cell transplant; CR = complete remission; HL = Hodgkin lymphoma; MC = multicenter; MTD = maximum tolerated dose; OL = open label; ORR = objective response rate; PR = partial remission; PTCL = peripheral T-cell lymphoma.

during the infusion of the second 1.8 mg/kg dose. One patient had an infusion-related reaction, but was able to receive the complete dose after recovering from the reaction. Peripheral neuropathy and adverse events related to neuropathy were reported in 16 patients, 13 of whom received the 1.8-mg/kg or 2.7-mg/kg dose. Typical presentation was grade 1 or grade 2 sensory neuropathy, such as numbness or tingling in the extremities, with the median time to onset of 9 weeks. Resolution of symptoms occurred in 63% (10 of 16) of patients. Three patients discontinued brentuximab vedotin therapy due to neuropathy.[2]

Therapy with this agent demonstrated positive initial results in a heavily pretreated patient population. Overall, brentuximab vedotin induced complete remission in 11 patients (24%), and objective responses occurred in 17/45 (38%) patients. Tumor regression was reported for 36 of 42 evaluable patients (86%). At the 1.8-mg/kg maximum tolerated dose, the objective response rate was 50% (6 of 12 patients), with 4 patients achieving complete remission and 2 patients with partial remission. The median duration of response was 9.7 months.[2]

Based on results of the positive Phase 1 data, Phase 2 studies were initiated to evaluate brentuximab vedotin in patients with relapsed or refractory HL and systemic ALCL. The efficacy and safety of this agent were studied in a single-arm multicenter study in patients with relapsed or refractory HL post ASCT.[19] Brentuximab vedotin 1.8 mg/kg was administered every 3 weeks for up to 16 cycles and the primary endpoint was the ORR; 102 patients were treated at 26 study sites. The median number of previous chemotherapy regimens was 4 and more than 70% of patients had primary refractory disease. Ninety-seven (95%) patients had a reduction in tumor size, and 83% of patients with B symptoms at baseline experienced resolution during brentuximab vedotin therapy. The ORR was approximately 73% (32% complete remission and 40% partial remission). Similar to Phase 1 study findings, common adverse events of any grade included peripheral sensory neuropathy, fatigue, nausea, neutropenia, diarrhea, and pyrexia (Table 2). Grade 3 events included neutropenia, peripheral sensory neuropathy, thrombocytopenia, and hyperglycemia. Grade 4 neutropenia was seen in 6% of patients and grade 4 thrombocytopenia, anemia, and abdominal pain were observed in 2%, 2%, and 1% of patients, respectively (Table 2).[17,19] Eighteen patients discontinued therapy because of an adverse reaction.[17,19]

Table 2. Brentuximab Vedotin Adverse Events in Phase 2 Trials

	Hodgkin Lymphoma, %[17,19]			Anaplastic Large Cell Lymphoma, %[17,20]		
Adverse Event	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Neutropenia	54	15	6	55	12	9
Anemia	33	8	2	52	2	
Thrombocytopenia	28	7	2	16	5	5
Peripheral sensory neuropathy	52	8		53	10	
Peripheral motor neuropathy	16	4		7	3	
Headache	19			16	2	
Dizziness	11			16		
Fatigue	49	3		41	2	2
Pyrexia	29	2		38	2	
Nausea	42			38	2	
Diarrhea	36	1		29	3	
Abdominal pain	25	2	1	9	2	
Vomiting	22			17	3	
Constipation	16			19	2	
Rash	27			31		
Pruritus	17			19		
Alopecia	13			14		
Cough	25			17		
Dyspnea	13	1		19	2	
Myalgia	17			16	2	
Back pain	14			10	2	
Pain in extremity	10			10	2	
Insomnia	14			16		

Another Phase 2 study was performed in patients with relapsed or refractory systemic ALCL.[20] This was a single-arm multicenter study that treated 58 patients. Brentuximab vedotin 1.8 mg/kg was administered every 3 weeks for up to 16 cycles of therapy. Half of the patients had primary refractory disease and 50% of patients had not responded to the most recent prior therapy. Most (70%) of the patients had ALK-negative disease. Results of the study showed an ORR of 86%; complete response was achieved in 57% of patients, and 29% achieved a partial remission. B symptoms resolved in 90% of patients who had symptoms at baseline. The most common adverse events of any grade were nausea, diarrhea, peripheral sensory neuropathy, pyrexia, dyspnea, fatigue, insomnia, and neutropenia (Table 2). Grade 3/4 adverse events included neutropenia, peripheral sensory neuropathy, diarrhea, and anemia (Table 2). Adverse events caused treatment discontinuations in 21% of patients.[17,20]

The role of brentuximab vedotin is being evaluated in a number of other trials. The AETHERA (High Risk of Residual Hodgkin Lymphoma Following Stem Cell Transplant) trial is a Phase 3 randomized, double-blind, placebo-controlled study of brentuximab vedotin and best supportive care versus placebo and best supportive care. In patients receiving

the study drug, interim results show 75% of patients having achieved an objective response, with 34% and 40% of patients achieving complete and partial remission, respectively. Tumor reductions were noted in 94% of the patients.[21] In addition to being the focus of the AETHERA trial, brentuximab vedotin is being studied in combination with multiagent chemotherapy in the treatment of HL and ALCL.

Adverse Reactions

Brentuximab vedotin treatment has been associated primarily with grade 1 or 2 toxicities. The most common adverse reactions (≥20%) have been neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, fever, rash, thrombocytopenia, cough, and vomiting. In addition, headache, dizziness, constipation, alopecia, myalgia, and insomnia have been reported in 10% or more of the patients.[17]

Two cases of anaphylaxis were reported in Phase 1 trials. Grade 1 or 2 infusion-related reactions were reported in 12% of patients during Phase 2 trials; common reactions included chills (4%), nausea (3%), dyspnea (3%), pruritus (3%), pyrexia (2%), and cough (2%).[2,18] No grade 3 or 4 infusion-related reactions were reported in Phase 2 trials.[17]

Serious adverse reactions were reported in 31% of patients in Phase 2 trials.[19,20] Peripheral motor neuropathy (4%), abdominal pain (3%), pulmonary embolism (2%), pneumonitis (2%), pneumothorax (2%), pyelonephritis (2%), and pyrexia (2%) were most commonly seen in patients with HL. Serious adverse reactions seen in patients with ALCL included septic shock (3%), supraventricular arrhythmia (3%), pain in extremity (3%), and urinary tract infection (3%). Progressive multifocal leukoencephalopathy (PML), Stevens-Johnson syndrome, and tumor lysis syndrome were seen in 1 patient each.[17]

The most common reasons for dose delays were neutropenia (14%) and peripheral sensory neuropathy (11%). Likewise, dose discontinuations due to peripheral sensory neuropathy and peripheral motor neuropathy occurred in 2 or more patients with HL or ALCL.[17]

Drug-Drug Interactions

Limited data are available on drug-drug interactions. However, MMAE does not appear to inhibit or induce any major CYP450 enzymes.[16] Coadministration of brentuximab vedotin with ketoconazole increased MMAE exposure by approximately 34%; this agent has not been studied with other potent CYP3A4 inhibitors. It is recommended that patients who are receiving concomitant strong CYP3A4 inhibitors be monitored closely for adverse reactions. Coadministration of the CYP3A4 inducer rifampin and brentuximab vedotin resulted in a 46% reduced MMAE exposure, although the clinical relevance of this decreased exposure is unknown.[17] When used at the approved dose of 1.8 mg/kg, brentuximab vedotin is not expected to clinically affect exposure to other drugs that are metabolized by major cytochrome P450 enzymes or are P-gp substrates.[16]

Precautions

Brentuximab vedotin warnings and precautions are detailed in the package insert. Patients should be monitored for peripheral neuropathy and the dose discontinued or modified as necessary. As with other antibody therapy, infusion-related reactions are possibile. If an infusion reaction occurs, the infusion should be stopped and the reaction treated. In the event of anaphylaxis, the infusion should be discontinued immediately. Dose delays, dose reductions, or therapy discontinuation may be necessary to manage grade 3 or 4 neutropenia. Stevens-Johnson syndrome, tumor lysis syndrome, and PML have each been reported once in early clinical trials. Lastly, brentuximab vedotin may cause fetal harm.[17]

Dosage, Preparation, and Administration

The FDA-approved brentuximab vedotin dose in both HL and ALCL patients is 1.8 mg/kg/dose administered as an intravenous infusion over 30 minutes every 3 weeks. Per the package insert, total body weight (up to a maximum of 100 kg) should be used to calculate the dose.[17] Treatment may be continued for a maximum of 16 cycles, or until disease progression or unacceptable toxicity occurs. Brentuximab vedotin is supplied as a 50-mg single-use vial. Each vial is reconstituted with 10.5 mL of sterile water for injection, USP, to obtain a 5-mg/mL concentration. Reconstituted brentuximab vedotin is then further diluted in 0.9% injection to achieve a final concentration of 0.4-1.8 mg/mL. Brentuximab vedotin should not be mixed or administered with other medications.[17] Premedication with acetaminophen, antihistamine, and a corticosteroid may be considered in patients who experience infusion-related reactions. No dosing recommendations are given for patients with renal or hepatic dysfunction.[17]

Formulary Recommendation

Given the available evidence, it is reasonable to add brentuximab vedotin to relevant formularies for its approved indication of relapsed/refractory HL after failure of ASCT and for relapsed/refractory ALCL; it offers clinicians an effective drug to use in a setting in which a standard of care is not well defined (relapsed/refractory disease). Its expense is significant; drug cost alone for 16 cycles of brentuximab vedotin therapy in a 70-kg patient is

currently estimated to be approximately $200,000.[22] Therefore, restricting its use to the outpatient formulary may be prudent at this time.

Summary

Phase 1 and Phase 2 trials have produced encouraging results for the treatment of relapsed or refractory HL and systemic ALCL disease with brentuximab vedotin. While ASCT may be curative when patients with HL relapse after initial therapy, treatment after ASCT failure is not standardized. Monotherapy with vinorelbine or gemcitabine is often used in this setting, but short durations of response and toxicity may limit their use. However, therapy with these agents is significantly less expensive than brentuximab vedotin therapy. It remains to be seen whether brentuximab vedotin will offer improved overall survival rates over single-agent vinorelbine or gemcitabine for relapsed or refractory HL. However, brentuximab vedotin has produced complete remission in heavily pretreated patients and should be considered after an unsuccessful ASCT or in patients who are not ASCT candidates and who have failed prior therapies. Therapy in relapsed/refractory ALCL is even less defined, as no standard of care exists in this setting. Rarely does single-agent therapy provide complete remission in the setting of relapsed and/or refractory disease; however, brentuximab vedotin results from early lymphoma trials have shown just that. In addition to having promising efficacy data, brentuximab vedotin has a favorable safety profile. Adverse events commonly observed are grade 1 or 2 toxicities and are typically managed through standard supportive care. Current and future studies will further elucidate brentuximab vedotin's role in lymphoma therapy, either as a single agent or in combination with other chemotherapy drugs. Brentuximab vedotin is an important new agent in the management of relapsed/refractory HL and ALCL.

Stephanie S Minich PharmD BCOP, Clinical Specialist, Hematology/Oncology, University of Michigan Health System, Ann Arbor, MI
Correspondence: Dr. Minich, staber@umich.edu
Reprints/Online Access: www.theannals.com/cgi/reprint/aph.1Q680

Conflict of interest: Author reported none

References

1. Hoppe RT, Mauch PT, Armitage JO, et al. Hodgkin lymphoma. 2nd ed. Philadelphia, PA: Lippincott Williams and Wilkins, 2007.
2. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. N Engl J Med 2010;363:1812-21.
3. Sureda A, Constans M, Iriondo A, et al. Prognostic factors affecting long-term outcome after stem cell transplantation in Hodgkin's lymphoma autografted after a first relapse. Ann Oncol 2005;16:625-33.
4. Majhail NS, Weisdorf DJ, Defor TE, et al. Long-term results of autologous stem cell transplantation for primary refractory or relapsed Hodgkin's lymphoma. Biol Blood Marrow Transplant 2006;12:1065-72.
5. Martinez C, Canals C, Allessandrino E, et al. Relapse of Hodgkin's lymphoma (HL) after autologous stem cell transplantation (ASCT): prognostic factors in 462 patients registered in the database of the EBMT (abstract). J Clin Oncol 2010;28(suppl):7s.
6. Ansell SM. Hodgkin lymphoma: 2011 update on diagnosis, risk-stratification, and management. Am J Hematol 2011;86:852-8.
7. Dearden CE, Johnson R, Pettengell R, et al. Guidelines for the management of mature T-cell and NK-cell neoplasms (excluding cutaneous T-cell lymphoma). Br J Haematol 2011;153:451-85.
8. Querfeld C, Khan I, Mahon B, Nelson BP, Rosen ST, Evens AM. Primary cutaneous and systemic anaplastic large cell lymphoma: clinicopathologic aspects and therapeutic options. Oncology 2010;24:574-87.
9. Savage KJ, Harris NL, Vose JM, et al. ALK-anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK + ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. Blood 2008; 111:5496-504.
10. Kewalramani T, Zelenetz AD, Teruya-Feldstein J, et al. Autologous transplantation for relapsed or primary refractory peripheral T-cell lymphoma. Br J Haematol 2006;134:202-7.
11. Deutsch YE, Tadmor T, Podack ER, Rosenblatt JD. CD30: an important new target in hematologic malignancies. Leuk Lymphoma 2011;52: 1641-54.
12. Foyil KV, Bartlett NL. Anti-CD30 antibodies for Hodgkin lymphoma. Curr Hematol Malig Rep 2010;5:140-7.
13. Katz J, Janik JE, Younes A. Brentuximab vedotin (SGN-35). Clin Cancer Res 2011;17:6428-36.
14. Okeley NM, Miyamoto JB, Zhang X, et al. Intracellular activation of SGN-35, a potent anti-CD30 antibody-drug conjugate. Clin Cancer Res 2010;16:888-97.
15. Younes A. CD30-targeted antibody therapy. Curr Opin Oncol 2011;23: 587-93.
16. Seattle Genetics. Data on file (014).
17. Package insert. Adcetris (brentuximab vedotin). Bothell, WA: SeattleGenetics, August 2011.
18. Fanale M, Forero-Torres A, Rosenblatt JD, et al. A phase 1 weekly dosing study of brentuximab vedotin in patients with relapsed/refractory CD30-positive hematologic malignancies. Clin Cancer Res 2012;18: 248-55.
19. Chen R, Gopal AK, Smith SE, et al. Results of a pivotal phase 2 study of brentuximab vedotin (SGN-35) in patients with relapsed or refractory Hodgkin lymphoma (abstract). Blood 2010;116:283.
20. Shustov AR, Advani R, Brice P, et al. Complete remissions with brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large cell lymphoma (abstract). Blood 2010;116:961.
21. Seattle Genetics, Inc. Seattle genetics and millennium report positive data from pivotal trial of brentuximab vedotin (SGN-35) in relapsed or refractory Hodgkin lymphoma at ASH annual meeting. Press release, December 6, 2010. www.seattlegenetics.com (accessed 2011 Oct 27).
22. AmerisourceBergen. www.amerisourcebergen.com/abc (accessed 2012 Feb 22).

Brentuximab Vedotin: Una Nueva era en el Tratamiento del Linfoma Hodgkin y del Linfoma Anaplásico de Células Grandes

SS Minich

Ann Pharmacother 2012;46:377-83.

EXTRACTO

OBJETIVO: Revisar los datos de los ensayos clínicos, farmacología, farmacodinámica, y efectos adversos de brentuximab vedotin.

FUENTES DE INFORMACIÓN: Se llevó a cabo una búsqueda bibliográfica a través de las bases de datos MEDLINE y PubMED (ambas 1966-octubre de 2011), así como en los extractos de la American Society of

Hematology (2000-enero de 2012), mediante los siguientes términos de búsqueda en inglés: brentuximab vedotin (brentuximab vedotin), SGN-35 (SGN-35), Hodgkin lymphoma (HL) (Linfoma de Hodgkin [LH]), y anaplastic large cell lymphoma (ALCL) (linfoma anaplásico de células grandes [LACG]).

SELECCIÓN DE FUENTES DE INFORMACIÓN Y MÉTODO DE EXTRACCIÓN DE INFORMACIÓN: En esta revisión se incluyeron estudios clínicos y extractos publicados y en curso escritos en lengua inglesa que detallaran la farmacología, farmacocinética, seguridad, y eficacia clínica de brentuximab vedotin en el tratamiento del LH y LACG.

SÍNTESIS: Brentuximab vedotin es un conjugado anticuerpo-fármaco (ADC) que combina cAC10, un anticuerpo anti-CD30, con el agente sintético anti-tubulina monometil auristatina E (MMAE). Un ensayo clínico de fase 1 en pacientes con LH o LACG sistémico recidivante o refractario apoyó una dosis de 1.8 mg/kg cada 3 semanas. El fármaco se toleró bien y la mayoría de las reacciones adversas tuvieron una intensidad de grado 1 o 2. Las toxicidades comunes incluyeron fatiga, pirexia, diarrea, náusea, neutropenia y neuropatía periférica. Los estudios de fase 2 en las mismas poblaciones de pacientes muestran tasas de respuesta objetiva (TRO) del 73-86% con un perfil de toxicidad aceptable. A partir de los resultados de estos ensayos de fase 2, la FDA concedió la autorización de brentuximab vedotin en agosto de 2011 para el tratamiento del LH o LACG recidivante o refractario.

CONCLUSIONES: Los datos del ensayo clínico de fase 1 y 2 indican que brentuximab vedotin es eficaz y seguro en pacientes con linfomas CD30 positivo recidivantes y refractarios. Este agente será objeto de estudio en combinación con quimioterapia para elucidar posteriormente su rol en la terapia del linfoma.

Traducido por Enrique Muñoz Soler

Brentuximab-vedotin: Une Nouvelle ère dans le Traitement du Lymphome de Hodgkin et du Lymphome Anaplasique à Grandes Cellules

SS Minich

Ann Pharmacother 2012;46:377-83.

RÉSUMÉ

OBJECTIF: Revoir les données cliniques, la pharmacologie, la pharmacocinétique et les effets indésirables du brentuximab-vedotin.

REVUE DE LA LITTÉRATURE: Une recherche dans les bases de données informatisées MEDLINE et PubMed (les 2 de 1966-octobre 2011), ainsi que dans les abrégés de l'American Society of Hematology (2000-janvier 2012) a été faite en utilisant les mots-clé brentuximab-vedotin, SGN-35, lymphome de Hodgkin (LH) et lymphome anaplasique à grandes cellules (LAGC).

SÉLECTION DES ÉTUDES ET DE L'INFORMATION: Toutes les études publiées ainsi que celles en cours et tous les abrégés publiés en anglais concernant la pharmacologie, la pharmacocinétique, l'innocuité et l'efficacité clinique du brentuximab-vedotin ont été inclus dans cet article de revue.

SYNTHESE DES DONNÉES: Le brentuximab-vedotin est un anticorps monoclonal, le brentuximab, conjugué à une immunotoxine appelée vedotin, une molécule anticancéreuse. Le brentuximab est un anticorps conçu pour se lier à un antigène, le CD30, qui s'exprime de façon préférentielle à la surface de certaines cellules caractéristiques du lymphome de Hodgkin, les cellules de Reed-Sternberg; utilisé seul, il est inefficace. Lié à la vedotin, le brentuximab permet au conjugué de se fixer sur les cellules de Reed-Sternberg. La vedotin est transportée à l'intérieur des cellules, se lie avec la tubuline, un composant du cytosquelette, ce qui provoque l'arrêt du cycle de division cellulaire et induit une apoptose. Un essai de phase I chez des patients présentant un LH réfractaire, une rechute de LH ou un LAGC diffus ont montré qu'une dose de 1,8 mg/kg aux 3 semaines était tolérée. Le profil d'innocuité de ce médicament était bon, la majorité des effets indésirables étant de grade 1 ou 2. Les effets les plus fréquents étaient : fatigue, pyrexie, diarrhées, nausées, neutropénies et neuropathies périphériques. Les études de phase II dans la même population ont montré des taux de réponse objective de 73-86% avec un profil de toxicité acceptable. En se basant sur ces études de phase II, la FDA a accordé une approbation en août 2011 au brentuximab-vedotin pour le traitement du lymphome de Hodgkin réfractaire ou lors de rechute et pour le lymphome anaplasique à grandes cellules.

CONCLUSIONS: Les données cliniques issues d'essais de phase I et II montrent que le brentuximab-vedotin est efficace et sécuritaire pour les patients ayant des rechutes ou des lymphomes réfractaires CD30 positifs. Cet agent est présentement sous étude en association avec la chimiothérapie afin de préciser son rôle dans le traitement des lymphomes.

Traduit par Denyse Demers