Cleveland Clinic Pharmacotherapy Update
From the Department of Pharmacy

Volume XV No. I January/February 2012

In This Issue:

Drug Information Service
(216) 444-6456, option #1

Comprehensive information about medications, biologics, nutrients, and drug therapy

Formulary Information

Medication Inservices

Brentuximab Vedotin: A Novel Therapy for Refractory Lymphomas

By: Anthony S. Zembillas, Pharm.D.

Introduction: Hodgkin's lymphoma (HL) is a cancer of the immune system characterized by the presence of Hodgkin's Reed-Sternberg (HRS) cells.[1] It affects approximately 7,350 new patients in the United States every year and is recognized as one of the most curable cancers.[2,3] Over the past 4 decades advances in treatment with combination chemotherapy and radiation therapy have led to promising cure rates as the estimated 5- and 10-year relative survival for patients with HL is 85% and 80%, respectively.[3,4] Unfortunately, 15-30% of patients with HL relapse after conventional therapy resulting in approximately 1,300 annual deaths in the United States.[3,5] Typically, autologous hematopoietic stem-cell transplantation (ASCT) is reserved for patients with recurrent or progressive HL after failing conventional therapy.[1,3] Despite the potential to cure, ASCT is estimated to be effective in only 50% of patients.[1] The prognosis for patients who relapse after ASCT is generally poor and is associated with a median survival of 26 months.[3,6] Patients who do not respond to ASCT have limited therapeutic options.[3]

Systemic anaplastic large cell lymphoma (sALCL) is a cancer of activated lymphocytes.[3] It is linked to phosphorylation of a tyrosine kinase, anaplastic lymphoma kinase (ALK), which results in uncontrolled growth of affected lymphoid cells. The heterogeneity of sALCL is characterized by the expression or absence of ALK.[7] Patients with sALCL who express ALK generally have a good prognosis as they respond well to combination chemotherapy. Conversely, those who do not express ALK usually have a worse outcome despite combination chemotherapy.[8] Patients who fail multi-agent chemotherapy regimens usually resort to ASCT which has the potential to cure. However, patients who relapse after ASCT generally have a poor prognosis.[3]

Brentuximab vedotin (Adcetris™; Seattle Genetics, Inc.) was developed in response to the paucity of treatment options available for HL and sALCL patients who have failed conventional chemotherapy and/or ASCT.[9] Based on response rates from two Phase II trials, brentuximab vedotin received accelerated approval from the U.S. Food and Drug Administration (FDA) in August 2011 for the following indications:[10]

1) Treatment of patients with HL after failure of ASCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates

2) Treatment of patients with sALCL after failure of at least one prior multi-agent chemotherapy regimen

Mechanism of Action: Brentuximab vedotin is an antibody-drug conjugate (ADC) consisting of a CD30-specific monoclonal antibody covalently

attached, via an enzyme-cleavable dipeptide linker, to monomethyl auristatin E (MMAE), a microtubular disrupting agent.[9] This novel ADC specifically suppresses the growth of CD30-containing cell lineages. CD-30 is a lymphotoxin receptor and member of the tumor necrosis factor (TNF) receptor superfamily.[10] It is highly expressed on neoplastic cells of HL and sALCL, but it is expressed minimally on normal lymphocytes making it an appealing chemotherapeutic target.[11,12] The ADC binds to the CD30 receptor on the cell surface forming an ADC-CD30 complex which becomes internalized.[9] Upon internalization into the cell, the dipeptide linker of the ADC-CD30 complex is cleaved and MMAE is liberated. Afterwards, MMAE binds to tubulin which arrests the cell cycle resulting in eventual apoptosis.

Pharmacokinetics: The pharmacokinetics of brentuximab vedotin are based on its three components: the ADC, total antibody, and MMAE.[9] Maximum concentrations of brentuximab vedotin were observed near the end of the 30 minute infusion. The estimated terminal half-life of the ADC is 4-6 days, achieving steady state concentrations within 21 days of administration. In vitro, the plasma protein binding of MMAE ranged from 68-82%; however, the compound is not expected to displace or be displaced by highly protein-bound drugs. Only a small proportion of MMAE undergoes metabolic transformation; this process occurs mainly through oxidation via the cytochrome P450 (CYP) 3A4/5 enzyme system. Clearance of MMAE appears to be dependent on its rate of release from the ADC. The majority of MMAE is eliminated unchanged in the feces.

Select Clinical Trials: Younes and colleagues performed a Phase II, single-arm, multicenter, open-label study which evaluated the efficacy and safety of brentuximab vedotin in 102 patients with relapsed or refractory HL.[9,13,14] Inclusion criteria were as follows: relapsed or refractory HL, age $\geq$ 12 years, measurable disease $\geq$ 1.5 cm, Eastern Cooperative Oncology Group (ECOG) score of 0-1, and prior ASCT.[13] The primary endpoint was the objective response rate (ORR), defined by the Revised Response Criteria for Malignant Lymphoma (RRCML) assessed by an independent review facility (IRF). Brentuximab vedotin was administered at a dose of 1.8 mg/kg every 3 weeks as a 30 minute outpatient intravenous (IV) infusion for up to 16 cycles. The median age of participants was 31 years (range 15-77), 87% were white, and 53% were female. Patients had received a median of 3.5 prior cancer-related systemic therapies excluding ASCT. Approximately 71% had primary refractory disease, while 42% had not adequately responded to their most recent therapy. Following treatment with brentuximab vedotin, a significant number of patients achieved a positive ORR. The results of the study are summarized in Table 1. Peripheral sensory neuropathy was noted in about 55% of those in the treatment arm; this side effect was resolved in the majority of patients with temporary dose delays and/or reductions to 1.2 mg/kg over a median time period of approximately 13 weeks.[13] The authors concluded that brentuximab vedotin produced durable ORRs in about 75% of patients with relapsed or refractory HL with manageable adverse events.

Advani and associates conducted a Phase II single-arm, multicenter, open-label trial which assessed the efficacy and safety of brentuximab vedotin in 58 patients with relapsed or refractory sALCL.[9,15,16] Inclusion criteria were as follows: relapsed or refractory systemic ALCL, age $\geq$ 12 years, measurable disease $\geq$ 1.5 cm with a positive fluorodeoxyglucose (FDG-avid) result, and ECOG score of 0-1.[15] The ORR, according to the RRCML assessed by an IRF, was the primary endpoint. Brentuximab vedotin was administered at a dose of 1.8 mg/kg every 3 weeks as a 30 minute outpatient IV infusion for up to 16 cycles. The median age of participants was 52 years (range, 14-76), 87% were white, and 57% were male. Patients had received a median of two prior cancer-related systemic therapies (range 1-6) and 72% had ALK negative sALCL. Approximately 62% had primary refractory disease and 50% were refractory to their most recent therapy, while 22% had not responded to any prior therapy. Around 45% had previously undergone radiation and 26% had a prior ASCT. A significant number of patients responded to brentuximab vedotin therapy. Results of the study are summarized in Table 1. Peripheral sensory neuropathy which occurred in about 45% of the patients was the most frequent drug-induced complication; however, it was reversible in 79% of those patients with dose delays and/or reductions to 1.2 mg/kg over a median time period of about 13 weeks.[15] The authors concluded that brentuximab vedotin produced a durable complete response in a significant proportion of patients with refractory sALCL and possessed a tolerable side effect profile.

Brentuximab vedotin received accelerated FDA approval based on the results of the aforementioned Phase II clinical trials.[9] Accelerated approval expedites the commercial release of drugs used to treat life-threatening illnesses.[17] Clinical trials submitted to the FDA for accelerated approval employ surrogate efficacy endpoints (e.g., ORR) which can be determined in a timely manner. In order for a drug to receive full FDA approval and remain on the market, the manufacturer is required to perform confirmatory studies utilizing more meaningful endpoints which take longer to assess (e.g., improved survival). Seattle Genetics is currently conducting the **A**DC **E**mpowered **T**rial for **H**odgkin to **E**valuate P**r**ogression after **A**SCT (AETHERA) trial to fulfill the FDA's final approval requirement.[18] This randomized, double-blind, placebo-controlled, multicenter, Phase III study will compare progression-free survival in about 325 post-ASCT patients treated with brentuximab vedotin with those receiving placebo.

Table 1: Efficacy Results in Patients with HL and sALCL[9]

	HL (n = 102)	sALCL (n = 58)
	Percent (95% CI)	
Complete response	32 (23, 42)	57 (44, 70)
Partial response	40 (32, 49)	29 (18, 41)
Objective response rate	73 (65, 83)	86 (77, 95)
	Median Duration of Response	
Complete response	20.5 months	13.2 months
Partial response	3.5 months	2.1 months
Objective response rate	6.7 months	12.6 months

HL = Hodgkin's Lymphoma sALCL = Systemic Anaplastic Large Cell Lymphoma CI = Confidence Interval
Complete Response = Disappearance of all evidence of disease
Partial Response = Regression of measurable disease; no new sites

Adverse Reactions: The most common adverse reactions (≥20%) observed in Phase II trials were neutropenia, thrombocytopenia, fatigue, anemia, peripheral sensory neuropathy, nausea, upper respiratory tract infection, diarrhea, abdominal pain, pyrexia, rash, cough, and vomiting.[9] Grade 1 or 2 infusion-related reactions were reported in 19 patients (12%) in Phase II trials and were associated with chills, nausea, dyspnea, pruritis, pyrexia, and cough. Anaphylaxis was also noted in two cases in Phase I trials, but not Phase II trials. Serious adverse reactions were observed in 31% of patients in Phase II trials. The incidence of the most common serious adverse reactions is listed in Table 2. Other significant serious events included one case each of progressive multifocal leukoencephalopathy (PML), Stevens-Johnson syndrome, and tumor lysis syndrome.

Table 2: Incidence of Serious Adverse Reactions[9]

HL (n = 102)		sALCL (n = 58)
Peripheral motor neuropathy (4%)	Pneumothorax (2%)	Septic shock (3%)
Abdominal pain (3%)	Pyelonephritis (2%)	Supraventricular arrhythmia (3%)
Pulmonary embolism (2%)	Pyrexia (2%)	Pain in extremity (3%)
Pneumonitis (2%)		Urinary tract infection (3%)

HL = Hodgkin's Lymphoma sALCL = Systemic Anaplastic Large Cell Lymphoma

Infusion Reactions: Although two cases of anaphylaxis were reported in Phase I trials, no Grade 3 or 4 infusion-related reactions were reported in Phase II trials.[9] However Grade 1 or 2 infusion-related reactions were reported for 19 patients (12%). The most common infusion-related manifestations were chills (4%), nausea (3%), dyspnea (3%), pruritis (3%), pyrexia (2%), and cough (2%).

Progressive Multifocal Leukoencephalopathy and Pulmonary Toxicity: The FDA recently sent healthcare professionals a Drug Safety Communication regarding brentuximab vedotin and the occurrence of PML; also included in this communication were concerns about the concurrent use of bleomycin causing pulmonary toxicity.[19] To date, there have been three reported cases of PML associated with brentuximab vedotin. Progressive multifocal leukoencephalopathy is a rare but serious brain infection that may result in death. The signs and symptoms of PML which may develop over the course of several weeks or months include changes in mood or usual behavior, confusion, thinking problems, loss of memory, changes in vision, speech, or walking, and decreased strength or weakness on one side of the body. Patients who develop any signs and symptoms of PML should notify their healthcare provider immediately. Brentuximab vedotin therapy should be held if PML is suspected and discontinued if a diagnosis is confirmed. A black-box warning about the risk of PML and a new contraindication involving the use of brentuximab vedotin with bleomycin will be added to the Adcetris™ package insert.

Drug Interactions: Monomethyl auristatin E, one of the components of brentuximab vedotin, is a substrate and inhibitor of CYP 3A4/5 enzymes.[9] Concomitant use of ketoconazole, a strong CYP3A4 inhibitor, produced an increase in MMAE exposure of about 34%; therefore, it is recommended that patients taking strong CYP3A4 inhibitors with brentuximab vedotin be carefully monitored for adverse events. Coadministration of rifampin, a potent CYP3A4 inducer, reduced exposure to MMAE by approximately 46%. Brentuximab vedotin has not been shown to affect serum levels of midazolam, a CYP3A4 substrate; therefore, it is not expected to significantly impact the metabolism of other CYP3A4 substrates.

Pregnancy and Lactation: Brentuximab vedotin is categorized as pregnancy-risk category D.[9] It has not been studied in pregnant women, but can cause fetal harm based on animal data. The drug has caused embryo-fetal toxicities, including decreased embryo viability and fetal malformations in animals. The potential hazard to the fetus should be explained to patients receiving brentuximab vedotin during pregnancy and to those who become pregnant while receiving the medication. It is unknown whether brentuximab vedotin is excreted through breast milk. The risks and benefits must be weighed when determining whether nursing mothers should continue therapy taking into account the importance of the drug to the mother.

Dose and Administration: The recommended dosing for brentuximab vedotin is 1.8 mg/kg given as an IV infusion over 30 minutes every 3 weeks.[9] Therapy is continued until a maximum of 16 cycles, disease progression, or intolerable toxicity is achieved. The maximum dose of brentuximab vedotin is 180 mg; the dose for patients >100 kg should be calculated utilizing a 100 kg weight. Patients should be closely monitored for infusion-related reactions. If anaphylaxis occurs, it is recommended to immediately and permanently discontinue brentuximab vedotin and administer appropriate medical therapy. If an infusion-related reaction occurs, the infusion should be stopped and appropriate medical management should be initiated. Patients with a history of an infusion-related reaction to brentuximab vedotin should receive premedication which may include acetaminophen, an antihistamine, and a corticosteroid for subsequent infusions.

Dose Modifications: Peripheral neuropathy and neutropenia should be managed using a combination of dose delay and dose reduction strategies.[9] For new or worsening Grade 2 or 3 neuropathy, brentuximab vedotin should be held until neuropathy improves to grade 1 or baseline and then restarted at 1.2 mg/kg. If Grade 4 peripheral neuropathy occurs, brentuximab vedotin should be discontinued. For Grade 3 or 4 neutropenia, the drug should be held until resolution to baseline or Grade 2 or lower. For subsequent cycles in patients who experience Grade 3 or 4 neutropenia, growth factor support should be considered**.** Despite the use of growth factors, discontinuation or a dose reduction to 1.2 mg/kg should be considered in patients with recurrent Grade 4 neutropenia.

Renal and Hepatic Impairment: The kidney and the liver are routes of elimination of MMAE, however the influence of renal or hepatic dysfunction on MMAE pharmacokinetics is unknown.[9] Dosage adjustments for patients with renal and/or hepatic impairment have not been established.

Formulary Status and Cost: Brentuximab vedotin was added to the CCHS Formulary in October of 2011. It is restricted to the Department of Hematology and Oncology for outpatient use only. Brentuximab vedotin is available in 50 mg vials and the average wholesale price of brentuximab vedotin is $5,400 per vial; therefore, the drug cost for a 70 kg patient would be approximately $16,200 (~3 vials) per dose.[20]

Conclusion: Upon initial evaluation most patients with HL and sALCL generally have a good prognosis; however, a subgroup of individuals eventually do not respond to conventional therapy leaving them with very limited treatment options. Brentuximab vedotin is a novel agent which has received accelerated FDA approval for the treatment of relapsing or refractory HL and sALCL disease states based on the promising results of two Phase II trials. In general, many of the drug's adverse events are manageable. Its dose-limiting toxicities (e.g., neutropenia, peripheral neuropathy) can usually be reversed through dose reductions and/or temporary delays in therapy. In Phase II trials, patients receiving brentuximab vedotin achieved significant improvement in their ORRs. However, supporting evidence from other confirmatory studies utilizing more concrete endpoints (e.g., survival, irreversible morbidity) is still needed to establish the drug's long-term efficacy. The results of the AETHERA trial will be critical in determining if brentuximab vedotin will improve overall survival.

References:

1. Younes A, Bartlett NL, Leonard JP, Kennedy DA, Lynch CM, Sievers EL, et al. Brentuximab vedotin (SGN-35) for relapsed CD-30 positive lymphomas. N Engl J Med 2010;363 (19):1812-21.
2. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, et al. Cancer Statistics, 2005. CA Cancer J Clin 2005;55:10-30.
3. Ansell SM. Brentuximab vedotin: delivering an antimitotic drug to activated lymphoma cells. Expert Opin Investig Drugs 2011;20(1):99-105.
4. Brenner H, Gondos A, Arndt V. Recent major progress in long-term cancer patient survival disclosed by modeled period analysis. J Clin Oncol 2007;25:3274-80.
5. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225-49.
6. Kewalramani T, Nimer SD, Zelenetz AD, Malhotra S, Qin J, Yahalom J, Moskowitz CH. Progressive disease following autologous transplantation in patients with chemosensitive relapsed or primary refractory Hodgkin's disease or aggressive non-Hodgkin's lymphoma. Bone Marrow Transplant 2003;32:673-9.
7. Medeiros LJ, Elenitoba-Johnson K. Anaplastic large cell lymphoma. Am J Clin Path 2007;127:707-22.
8. Savage KJ, Harris NL, Vose JM, Ullrich F, Jaffe ES, Connors 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.
9. Adcetris™ package insert. Bothell, WA: Seattle Genetics, Inc; 2012 January.
10. Brentuximab Vedotin. Available at http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm268969.htm. Accessed: October 19, 2011.
11. Mir SS, Richter B, Duckett CS. Differential effects of CD30 activation in anaplastic large cell lymphoma and Hodgkin disease cells. Blood 2000;96(13):4307-12.
12. Nagata S, Ise T, Onda M, Nakamura K, Ho M, Raubitschek A, Pastan H. Cell membrane-specific epitopes on CD30: potentially superior targets for immunotherapy. PNAS 2005;102(22):7946-51.
13. Younes A, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Durable complete remissions in pivotal phase 2 study of SGN-35 (brentuximab vedotin) in patients with relapsed or refractory Hodgkin lymphoma (HL). Presented at the International Conference on Malignant Lymphoma June 2011.
14. Chen RW, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ. Results from a pivotal phase II study of brentuximab vedotin (SGN-35) in patients with relapsed or refractory Hodgkin lymphoma (HL). J Clin Oncol 29:2011 (suppl:abstr 8031).
15. Advani R, Shustov A, Brice P, Barlett NL, Rosenblatt JD, Illidge T, et al. Brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma: a phase 2 study update. Presented at the American Society of Hematology December 2011.
16. Pro B, Advani R, Brice P, Barlett N, Rosenblatt JD, Illidge T, et al. Durable remissions with brentuximab vedotin (SGN-35): updated results of a phase II study in patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL). J Clin Oncol 29:2001 (suppl;abstr 8032).
17. Accelerated approval. Available at http://www.medscape.com/viewarticle/449551 4. Accessed: January 1, 2012.
18. Seattle Genetics, Takeda, and Millennium announce initiation of phase III AETHERA trial of brentuximab vedotin (SGN-35) for post-transplant Hodgkin lymphoma. Available at www.takeda.com/press/article_35923.html Accessed: January 1, 2012.
19. Adcetris (brentuximab vedotin): Drug safety communication-progressive multifocal leukoencephalopathy and pulmonary toxicity. Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm287710.htm Accessed: January 20, 2012.
20. AmeriSourceBergen Wholsaler Located at: www.amerisourcebergen.com Accessed: February 6, 2012.

Drug Information Center

Frequently Asked Question

Question: Can a patient with low IgA levels receive intravenous immune globulin (IVIG)?

Answer: In general, patients with low or deficient IgA levels may receive IVIG which is IgA-depleted. The current formulary agent, Gammagard Liquid 10% (Baxter Healthcare Corporation), is considered IgA-depleted with < 37 mcg/mL of IgA. It is important to verify what product is to be used for the patient as IgA content varies from product to product.

The patient should be closely monitored during administration, since there is a risk of reaction. If the patient previously had an adverse reaction to an IVIG infusion, premedication with an antihistamine, corticosteroid, or nonsteroidal anti-inflammatory drug (NSAID) may be needed.

Caution: If the patient is **IgA deficient with antibodies against IgA and a history of hypersensitivity,** Gammagard Liquid 10% administration is **contraindicated.** Anaphylaxis has been reported with IV administration and may be possible with subcutaneous administration. These patients are at higher risk of developing severe hypersensitivity and anaphylactic reactions. Management of these reactions includes discontinuing the IVIG infusion immediately and initiating supportive care.

References

1. Product Information. Gammagard Liquid [Immune Globulin Infusion (Human)] 10%. Westlake Village, CA: Baxter Healthcare Corporation; July 2011.
2. Stein MR. The new generation of liquid intravenous immunoglobulin formulations in patient care: a comparison of intravenous immunoglobulins. Postgrad Med 2010;122(5):176-84.