Brentuximab Vedotin: A CD30-Directed Antibody-Cytotoxic Drug Conjugate

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Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL), which is a subtype of non-Hodgkin lymphoma, are relatively uncommon lymphoproliferative types of cancer. These malignancies are highly curable with initial treatment. Nonetheless, some patients are refractory to or relapse after first- and second-line therapies, and outcomes for these patients are less promising. Brentuximab vedotin is a CD30-directed antibody-cytotoxic drug conjugate that has demonstrated efficacy in response rates (objective response rates and complete response) when given to patients with refractory or relapsed HL and sALCL. Although not compared directly in clinical trials, the response rates with brentuximab vedotin are higher than those of several current treatments for refractory or relapsed HL and sALCL. Adverse effects associated with brentuximab vedotin are considered manageable. Nonetheless, several serious adverse effects (e.g., neutropenia, peripheral sensory neuropathy, tumor lysis syndrome, Stevens-Johnson syndrome, and progressive multifocal leukoencephalopathy, resulting in death) have been reported with its use. Despite a lack of survival and patient reported outcome data, the United States Food and Drug Administration (FDA) granted accelerated approval to brentuximab vedotin for the treatment of HL after failure of autologous stem cell transplantation or at least two combination chemotherapy regimens, and for sALCL after failure of at least one combination chemotherapy regimen. With this approval, brentuximab vedotin is the first FDA-approved agent for the treatment of HL in over three decades and the first agent specifically indicated to treat sALCL. Results of ongoing prospective trials should determine if brentuximab vedotin has a survival benefit when compared directly with standard treatment and if brentuximab vedotin is safe and efficacious when given earlier in the disease process, or when used with other chemotherapy for the treatment of HL and sALCL or other CD30-positive malignancies.

Key Words: anaplastic large cell lymphoma, brentuximab vedotin, Hodgkin lymphoma, SGN-35.

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Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL), which is a subtype of non-Hodgkin lymphoma, are relatively uncommon lymphoproliferative types of cancer.[1, 2] It is estimated that over 8800 Americans are diagnosed with HL each year, whereas the incidence of sALCL is far lower at approximately 2000 cases each year.[3] Classic HL is primarily characterized by the presence of multinucleated Reed-Sternberg cells that express CD30 and CD15 in an inflammatory cellular background. Similarly, sALCL, which is classified by presence or absence of

anaplastic lymphoma kinase (ALK), also expresses a uniform CD30-positive immunophenotype.[1, 2] Although similar in morphology and immunophenotype, ALK-positive subtypes, which account for more than 50% of cases of sALCL, differ from ALK-negative subtypes in their degree of tyrosine kinase activation, CD30 transcription, and oncogenic effect.[4, 5]

HL and sALCL are considered highly curable cancers, with overall 5-year survival rates of 83–90% for HL and 49% (ALK-negative subtype) to 80% (ALK-positive subtype) for sALCL.[3, 5] Approximately 10–20% of patients with HL will be refractory to or relapse after first-line therapies.[6] These patients are typically treated with high-dose chemotherapy and autologous stem cell transplantation (HDC-ASCT) with or without radiation therapy. Patients who do not respond or who relapse to ASCT generally have a poor prognosis, with an estimated median survival of less than 3 years.[7–10] Regimens for these patients include salvage chemotherapy, reduced-intensity allogeneic stem cell transplantation, or enrollment in a clinical trial.[1] Unfortunately, the salvage chemotherapy regimens have relatively low response rates (Table 1).[11–17] Treatment of refractory or relapsed sALCL can also be challenging. This is especially true of ALK-negative disease, which is generally less responsive to chemotherapy than ALK-positive sALCL.[5] According to the National Comprehensive Cancer Network (NCCN) clinical practice guidelines for non-Hodgkin lymphoma, patients with either type of sALCL who fail first-line therapy and who are candidates for transplantation should receive HDC-ASCT or allogeneic SCT, with or without second-line chemotherapy before transplantation. For patients who are not transplantation candidates, the guidelines generally recommend enrollment in a clinical trial.[2] Similar to HL, failure to respond to second-line therapy or transplantation is associated with a poor prognosis. Indeed, the 5-year progression-free survival (PFS) rate in those with relapsed or refractory ALK-positive and ALK-negative sALCL who underwent transplantation is only 58% and approximately 25%, respectively.[18, 19] Novel therapies are needed to fill the void of therapeutic options for patients with refractory or relapsed HL and sALCL.

Brentuximab vedotin (Adcetris; Seattle Genetics, Inc., Bothell, WA), previously referred to as SGN-35, is a CD30-directed antibody-cytotoxic drug conjugate that has reported efficacy for response rates in two key clinical trials that enrolled patients with refractory or relapsed CD30-positive lymphomas (i.e., HL and sALCL).[20, 21] Although not compared directly in clinical trials, many of the response rates with brentuximab vedotin are much higher than those reported with treatments currently used as salvage therapy for relapsed or refractory HL or as second-line therapy for sALCL. In August 2011, despite a lack of survival or patient-reported outcome data, the United States Food and Drug Administration (FDA) granted accelerated approval to brentuximab vedotin for the treatment of HL after failure of ASCT or at least two combination chemotherapy regimens, and for sALCL after failure of at least one combination chemotherapy regimen.[22, 23] With this approval, brentuximab vedotin is the first FDA-approved agent for the treatment of HL in over three decades, and the first drug specifically indicated to treat sALCL.[23]

CD30

CD30 was discovered in 1982 and identified as a transmembrane receptor protein belonging to the tumor necrosis factor receptor superfamily.[24] The protein has limited expression on healthy tissues; rather, CD30 is primarily expressed on the surface of malignant Reed-Sternberg cells in HL, sALCL cells, embryonal carcinomas, various T cell cancers, and other hematologic malignancies. Moreover, expression of CD30 is associated with T cell activation, and its signaling affects cellular proliferation, differentiation, and survival. Because of these characteristics, CD30 is a primary target in various cancers.[25, 26]

Mechanism of Action

Antibody drug conjugates (ADCs) combine a targeted monoclonal antibody therapy with a cytotoxic agent. Brentuximab vedotin is an ADC that covalently links monomethyl auristatin E (MMAE), an antimicrotubule agent, to the

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Table 1. Salvage Chemotherapy Regimens for Patients with Relapsed Hodgkin Lymphoma[11–17]

Regimen	Complete Response (%)	Partial Response (%)	Overall Response Rate (%)	Progression-free Survival (mo)	Overall Survival (mo)
Vinblastine[11, a](n=17)	12	47	59	8.3	38.8
Vinorelbine[12, b](n=24)	14	36	50	NR	NR
Gemcitabine[13, c](n=27)	0	22	22	6.4	26.9
Vinorelbine + gemcitabine[14, d](n=8)	50	25	75	NR	NR
Rituximab[15, e](n=22)	5	18	22	NR	NR
Rituximab + gemcitabine[16, f](n=33)	15	33	48	2.7	NR
Panobinostat[17, g](n=129)	3	22	26	NR	NR

NR = not reported; Overall response rate = complete response + partial response.
[a]Vinblastine 4–6 mg/m^2 every 1–2 wks until disease progression.
[b]Vinorelbine 30 mg/m^2 every wk (× 4 cycles).
[c]Gemcitabine 1250 mg/m^2 on days 1, 8, and 15 every 4 wks (× 2 cycles).
[d]Vinorelbine 25 mg/m^2 + gemcitabine 1000 mg/m^2 on days 1 and 8 every 3 wks (× at least 2 cycles).
[e]Rituximab 375 mg/m^2 every wk (× 6 cycles).
[f]Gemcitabine 1250 mg/m^2 on days 1 and 8 every 3 wks (× 2 cycles) + rituximab 375 mg/m^2 every wk (× 6 cycles).
[g]Panobinostat 40 mg 3 times/wk every wk for 3-wk cycles (× at least 2 cycles).

CD30-specific chimeric immunoglobulin G1 monoclonal antibody by an enzyme-cleavable dipeptide linker (Figure 1).[22, 25] Once ADC binds to CD30 on the cell surface, it is rapidly internalized and transported to lysosomes. Inside the cell, the peptide linker is selectively cleaved, thereby releasing free MMAE to bind tubulin. This binding disrupts the microtubule network, prompts arrest of the G2/M phase of the cell cycle, and results in apoptosis of the CD30-expressing tumor cell.[22]

Pharmacokinetics

A multicenter phase I trial evaluated pharmacokinetic parameters of the three components of brentuximab vedotin (i.e., ADC, MMAE, and total antibody).[27, 28] This study showed that total antibody and ADC had similar pharmacokinetic profiles; therefore, only results for ADC and MMAE were reported. After administration of a 1.8 mg/kg intravenous infusion of brentuximab vedotin, the time to maximum concentration (T_{max}) of ADC was immediate, but occurred 2–3 days later for MMAE. The terminal half-life for these two components ranged from 4–6 days and 3–4 days, respectively. When brentuximab vedotin was given every 3 weeks, which is the FDA-approved dosing schedule,[22] similar steady-state concentrations were achieved within 21 days, and there was no accumulation of either ADC or MMAE. Finally, it was shown that the area under the concentration-time curve for ADC and MMAE is dose-proportional.[22, 28]

In another phase I dose-escalation trial, similar pharmacokinetic data were reported for T_{max},

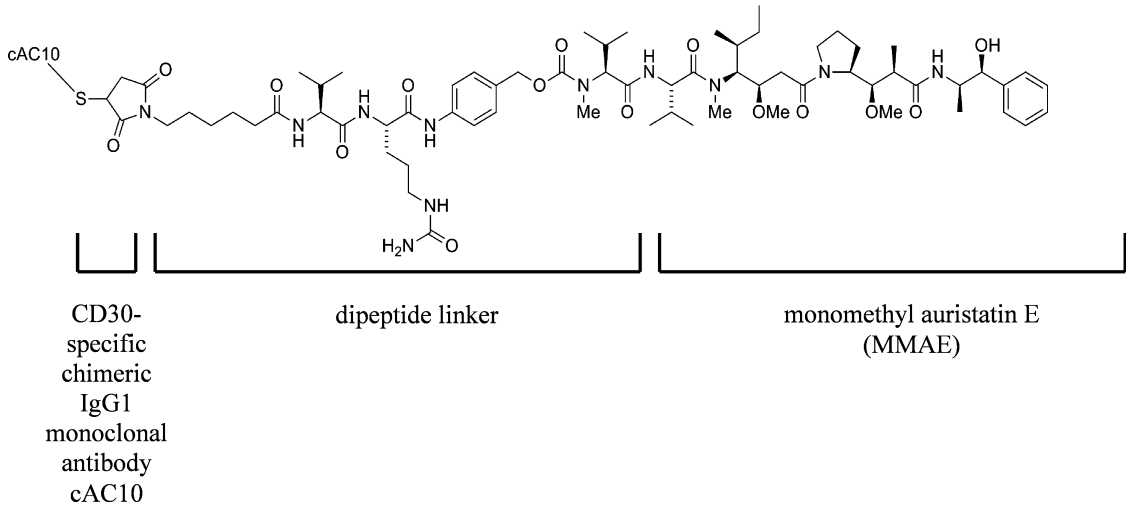

Figure 1. Chemical structure of brentuximab vedotin.

half-life, and steady-state concentration when brentuximab vedotin 0.4–1.4 mg/kg was administered once/week (days 1, 8, and 15 of each 28-day cycle).[29] However, moderate accumulation was observed with weekly administration, which is consistent with the terminal half-life. This ADC has a steady-state volume of distribution ranging from 6–10 L, and other in vitro data have shown that MMAE is approximately 68–82% protein bound, undergoes oxidation by cytochrome P450 (CYP) 3A4 and CYP3A5 to a small extent, and is eliminated unchanged in the feces and urine over a 7-day period.[22]

Clinical Efficacy Trials

Relapsed or Refractory Hodgkin Lymphoma and Systemic Anaplastic Large Cell Lymphoma

The first phase II trial evaluating the efficacy of brentuximab vedotin was a multinational, open-label, single-arm study.[20, 30] It enrolled 102 patients who had refractory or relapsed HL and had previously received HDC-ASCT. Patients were eligible if they were at least 12 years old and had CD30-positive disease, measurable disease that was at least 1.5 cm by computed tomography and fluorodeoxyglucose (FDG)-avid by positron emission tomography, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 (indicating a good performance status). Patients also had to have an absolute neutrophil count of at least 1000 cells/mm^3, platelet count of at least $50 \times 10^3/mm^3$, serum creatinine 1.5 times the upper limit of normal (ULN) or less, and alanine aminotransferase and aspartate aminotransferase levels 2.5 times the ULN or less. Patients who were pregnant, had a previous allogeneic SCT, had New York Heart Association class III or IV congestive heart failure, had cerebral or meningeal disease, had active infection, or received treatment with corticosteroids (equivalent to $\geq$ 20 mg/day of prednisone) were excluded. Patients had been treated with a median of 3.5 (range 1–13) previous chemotherapy regimens in addition to ASCT. Brentuximab vedotin 1.8 mg/kg was administered as a 30-minute intravenous infusion every 3 weeks for up to 16 cycles in an outpatient setting. The primary efficacy end point was objective response rate (ORR) in the intent-to-treat population. The ORR was the total number of patients who achieved a complete response or partial remission, which was defined as tumor shrinkage of at least 50%, as confirmed by an independent review facility according to revised response criteria for malignant lymphoma.[31] Secondary end points included complete response rate, duration of response, overall survival, and PFS. Patients in the study received a median of nine cycles of treatment (range 1–16 cycles) with a median dose intensity of 96%. The independent review facility reported that 76 (75%) of the 102 patients achieved an ORR (95% confidence interval [CI] 64.9–82.6%), whereas 34 patients (33%) achieved complete response.[17, 30] Partial remission was reported in 41 patients (40%) who achieved an ORR. Median duration of the ORR was 6.7 months (95% CI 3.6–14.8 mo), and median duration of complete response was 20.5 months (95% CI 10.8 mo to not estimable). Ninety-six patients (94%) experienced tumor reductions with an overall disease control rate (complete response plus partial remission plus stable disease) of 96% (95% CI 90.3–98.9%). The estimated median PFS was 5.6 months (95% CI 5.0–9.0 mo) for all patients; however, for patients who achieved complete response and did not undergo allogeneic SCT, the median PFS was 21.7 months. Estimated 12-month survival was 89% (95% CI 83–95%) for all patients.[17] Furthermore, an estimated 24-month survival has been reported as 65% (95% CI 55% to 74%). Median overall survival was 31.6 months for patients who achieved partial remission 20.6 months for patients with stable disease, and 10.2 months for patients with progressive disease. Overall survival has not been reached for patients that achieved a complete response.[30] Limitations of this study included the phase II, single-arm study design, without direct comparison. The sample size was also relatively small. In addition, the primary end point investigated was ORR rather than overall survival. Median duration of complete response was likely difficult to evaluate, as the trial did not require FDG-positron emission tomography scans after cycle 7.

Another phase II study with the same methods as the previously described study, evaluated the efficacy of brentuximab vedotin in 58 patients with refractory or relapsed sALCL.[21, 32] Eligible patients were at least 12 years old, had CD30-positive disease, measurable disease that was 1.5 cm or more FDG-avid and an ECOG performance status of 0–1, and had received at least one previous treatment with curative intent. The majority (72%) of patients in this study were ALK negative. Exclusion criteria consisted of previous treatment with brentuximab vedotin, previous allogeneic SCT, and pregnancy.

Enrolled patients had received a median of two systemic cancer-related treatment regimens (range 1–6), with approximately 26% of these patients receiving prior ASCT. The primary efficacy outcome was ORR (complete response plus partial remission) as determined by the independent review facility in an intent-to-treat population. Secondary efficacy end points were complete response rate, duration of response, PFS, and overall survival. Patients received a median of seven treatment cycles (range 1–16). Fifty (86%) of the 58 patients achieved an objective response (95% CI 74.6–93.9%) and 34 patients (59%) achieved complete response. Of the patients who achieved an objective response or a complete response, the median time to response was 5.9 weeks (range 4.3–14 wks) and 11.9 weeks (range 5.1–50.3 wks), respectively, whereas the median duration of response was 12.6 months (95% CI 5.7 mo to not estimable) and 13.2 months (95% CI 10.8 mo to not estimable), respectively. A reduction from baseline in tumor size was found in 56 patients (97%). The median PFS was 14.6 months; however, median overall survival has yet to be reached as additional results are pending. At the time of analysis, the 12-month survival rate was estimated at 70%. A number of limitations to this study exist. First, the study is only phase II, used a single-arm design without direct comparison, and enrolled a small number of patients. Second, the primary end point consisted of a surrogate marker, ORR, rather than overall survival. Finally, overall survival results were not reached or available at the time of publication.

Prevention of Relapse for Hodgkin Lymphoma

Promising results from phase II trials provided support to investigate the use of brentuximab vedotin earlier in the disease course for patients with refractory or relapsed HL, specifically to prevent relapse after ASCT. The AETHERA study is an ongoing, double-blind, randomized, placebo-controlled, multicenter, phase III trial investigating the efficacy and safety of brentuximab vedotin in combination with best supportive care compared with placebo and best supportive care in patients who are at high risk of residual HL after ASCT.[33] Investigators hope to enroll 322 patients. Eligible patients must be at least 18 years of age, have an ECOG performance status of 0–1, have high-risk classic HL (defined as history of refractory HL, relapsed or progressive HL that occurs less than 1 year from the end of treatment with first-line chemotherapy or combination treatment, and extranodal involvement when pre-ASCT relapse occurs), and have received an ASCT within 30–45 days of enrollment. Patients will receive brentuximab vedotin 1.8 mg/kg or placebo on day 1 of each 21-day cycle for up to 16 cycles. The primary end point is PFS, with secondary end points of overall survival, safety and tolerability, and immunogenicity. The estimated target date for primary outcome completion is June 2013, with an estimated study completion date of April 2016.

Initial Therapy for Hodgkin Lymphoma

Clinical trials are also investigating the efficacy of brentuximab vedotin as initial treatment in patients with CD30-positive malignancies. Interim results for an ongoing, phase I, open-label, multicenter study evaluating the addition of brentuximab vedotin to frontline standard therapy for HL (doxorubicin plus bleomycin plus vinblastine plus dacarbazine [ABVD]) or a modified standard therapy (doxorubicin plus vinblastine plus dacarbazine [AVD]) in patients with newly diagnosed advanced-stage HL were recently released.[34, 35] In this study brentuximab vedotin is being administered in doses of 0.6, 0.9, or 1.2 mg/kg in combination with ABVD or 1.2 mg/kg in combination with AVD, both given on days 1 and 15 of a 28-day cycle for up to six cycles. Outcomes include evaluation of a dose-limiting toxicity period and ORR. To date, 51 patients have been assessed (25 received brentuximab vedotin plus ABVD, and 26 received brentuximab vedotin plus AVD). Twenty-two of the 25 patients completed frontline therapy with brentuximab vedotin plus ABVD, and of these, 21 achieved complete response. Twenty-five patients completed therapy with brentuximab vedotin plus AVD. Of these patients, 23 achieved complete response and 1 achieved PR at the end of therapy.[34, 35] No dose-limiting toxicities were reported with brentuximab vedotin at its maximum dose of 1.2 mg/kg every 14 days. Nonetheless, 11 patients (44%) treated with brentuximab vedotin plus ABVD experienced pulmonary toxicity; therefore, bleomycin was removed from the treatment regimen. Seven of the 11 patients discontinued bleomycin therapy and completed treatment with brentuximab vedotin plus AVD. Thus far, no pulmonary toxicity events have been reported in those receiving brentuximab vedotin plus AVD. An expansion cohort of approximately 20 patients is being conducted to

evaluate brentuximab vedotin 1.2 mg/kg in combination with AVD therapy.[34, 36]

Preallogeneic Stem Cell Transplantation for Hodgkin Lymphoma

Allogeneic SCT is a potentially curative option for some patients who relapse after ASCT. Yet patients are still at risk for relapse after allogeneic SCT, especially those who have poorly controlled disease. It is hypothesized that brentuximab vedotin use in the preallogeneic SCT setting could improve pretransplantation disease control and, in turn, improve allogeneic SCT outcomes.[37, 38] A retrospective analysis reviewed patients with relapsed or refractory HL who received brentuximab vedotin before undergoing reduced-intensity allogeneic SCT.[37] The study included 54 patients with relapsed disease who received brentuximab vedotin, with the intent of subsequent allogeneic SCT as a potential cure. Eighteen of these patients did receive allogeneic SCT. A total of 36 patients did not proceed to transplantation; 7 due to persistent residual disease, 4 due to no donor, 18 due to patient preference, and 7 due to comorbidities or advanced age. All patients who received brentuximab vedotin before transplantation achieved engraftment as well as over 99% donor chimerism. The median time to neutrophil recovery was 14 days, defined by an ANC > 500 cells/mm^3. The investigators did not observe an increased frequency of transplant toxicity or acute and chronic graft-versus-host disease (GVHD). Patients were followed for 1 year and had a reported PFS of 92.3% and overall survival of 100% after allogeneic SCT. As this was a retrospective review with short follow-up, additional studies need to be conducted to define the role of brentuximab vedotin use before allogeneic SCT.

A case series of 15 patients who received brentuximab vedotin as cytoreductive therapy before allogeneic SCT was published.[38] All patients achieved an objective response before allogeneic SCT, with 12 patients (80%) achieving complete response. Thirteen patients (87%) continued to be in remission at the time of the report and are being followed posttransplantation. The results of this publication are currently only available in abstract form and further results are forthcoming.

Postallogeneic Stem Cell Transplantation for Hodgkin Lymphoma

In addition to cytoreduction before allogeneic SCT, brentuximab vedotin has been investigated in patients with relapsed HL after allogeneic SCT. A cohort of 25 patients who had relapsed or refractory HL or who had progressed after at least one systemic salvage chemotherapy and after allogeneic SCT with measureable disease was evaluated from open-label, nonrandomized trials.[39] Exclusion criteria consisted of allogeneic SCT within 100 days or ASCT within 4 weeks, any grade of acute or chronic GVHD, concurrent corticosteroids equivalent to 20 mg/day or more of prednisone, active infection requiring antimicrobial therapy within 2 weeks, an ANC less than 1000 cells/mm^3, platelet count less than 50×10^3/mm^3, or performance status greater than 1. Patients received a 30-minute intravenous infusion of brentuximab vedotin at doses of 1.2 mg/kg (6 patients) or 1.8 mg/kg (19 patients) every 3 weeks. Four of the six patients who received 1.2 mg/kg initially had their doses increased to 1.8 mg/kg during the extension phase. Treatment with brentuximab vedotin continued until disease progression or unacceptable toxicity.

Patients in the study had a median total of nine prior treatment regimens, a median time of 12.5 months to disease progression after allogeneic SCT and a median of three treatment regimens after allogeneic SCT. The median time to first dose of brentuximab vedotin was 42 months (range 6–116 mo), with a median of eight cycles (range 1–16 cycles) of brentuximab vedotin administered. At the time of evaluation, 19 patients had discontinued treatment. Reasons for discontinuation included disease progression (8 patients), adverse event (9 patients), investigator decision (1 patient), and completion of treatment (1 patient). Of the 24 patients who were evaluable for response, 12 (50%) had an objective response, 9 (38%) achieved complete response, and 3 (13%) achieved partial remission. The median time to complete response was 10.7 weeks (range 6.3–32 wks) and the median PFS was 7.8 months. At the time of publication, the median overall survival had not yet been reached. Limitations of this study include the fact that it was an open-label, nonrandomized study with a small number of patients. Patients also received brentuximab vedotin at differing doses, with some patients receiving additional treatment cycles as part of an extension study. In addition, patients were excluded if they were within 100 days of allogeneic SCT or if they had GVHD; this exclusion decreases the external validity of the study, as this high-risk population would be of clinical interest in examining the safety and efficacy of brentuximab vedotin.

Other Areas of Research

Due to its unique mechanism of action, brentuximab vedotin is being evaluated as treatment for a number of other CD30-positive malignancies including mature T cell and natural killer–cell neoplasms, nonlymphomatous malignancies, and non-Hodgkin lymphoma. Other diseases for which brentuximab vedotin is being studied include mycoses fungoides, extensive lymphomatoid papulosis, Sézary syndrome, systemic mastocytosis, T-cell prolymphocytic leukemia, and primary effusion lymphoma. Studies evaluating brentuximab vedotin in children with HL or sALCL are also under way.[40–43]

Adverse Effects

Brentuximab vedotin is associated with manageable adverse effects. Although the majority of adverse effects are primarily grade 1 or 2 in severity, approximately half of the patients in phase II trials experienced at least one treatment-emergent grade 3 or 4 reaction.[20, 21] In these trials, 160 patients (102 with HL and 58 with sALCL) received brentuximab vedotin monotherapy 1.8 mg/kg every 3 weeks for a maximum of 56 weeks. Adverse effects that were reported in more than 25% of the patients with HL or sALCL, respectively, included neutropenia (54% and 55%), peripheral sensory neuropathy (52% and 53%), fatigue (49% and 41%), nausea (42% and 38%), diarrhea (36% and 29%), anemia (33% and 52%), pyrexia (29% and 38%), and rash (27% and 31%). Adverse effects that reached a grade 3 or 4 severity included anemia, thrombocytopenia, peripheral neuropathy, and neutropenia, which could be prolonged ($\geq$ 7 days).[20–22] Brentuximab vedotin–induced peripheral neuropathy is considered cumulative and generally reversible. The majority of the patients who experienced any grade of peripheral neuropathy in phase II trials had some degree of resolution (49% complete resolution, 31% partial, and 20% none).[20, 21] Because of the severity and seriousness of these adverse effects, product labeling recommends dose delays, dosage reduction, or drug discontinuation for managing neutropenia and peripheral neuropathy (Table 2).[22]

Infusion-related reactions have been reported during brentuximab vedotin administration. In a phase I trial, 2 (2%) of 91 patients experienced anaphylaxis; however, in phase II trials, only grade I or II infusion-related reactions (chills, nausea, dyspnea, pruritus, pyrexia, and cough) were reported in 19 (12%) of 160 patients.[19–21, 27] Brentuximab vedotin therapy should be immediately discontinued if anaphylaxis occurs. In addition, for patients who experience an infusion-related reaction, acetaminophen, an antihistamine, and a corticosteroid should be given before subsequent infusions are administered (Table 2).[22]

Other serious adverse effects rarely reported during premarketing trials with brentuximab vedotin include tumor lysis syndrome (primarily noted with initial doses in patients with bulky or rapidly proliferating disease), Stevens-Johnson syndrome (in one patient, but the case was confounded by recent history of naproxen use), and progressive multifocal leukoencephalopathy (PML), in one patient.[22] In January 2012, the FDA released a safety notice that detailed two additional cases of John Cunningham (JC) virus infection resulting in PML, and subsequent death in patients who received brentuximab vedotin. Because of these new cases of PML, a black-box warning highlighting this risk was added to the drug's product labeling.[44]

Immunogenicity

In phase II trials, positive antibody formation that is directed against the antibody component of brentuximab vedotin occurred.[20, 21] Transient ($\leq$ 2 positive results from baseline) or persistent ($>$ 2 positive results from baseline) antibody formation was reported in 42 (27%) and 11 (7%) of the 157 treated patients, respectively, of whom 8 (5%) already had positive antibody formation at baseline.[20–22]A higher frequency of infusion-related reactions was noted overall in patients who had persistent antibody formation. Of those who experienced persistent positive antibodies, two patients had infusion-related reactions that resulted in discontinuation of brentuximab vedotin.[19–21] Although population pharmacokinetic analyses showed that antibody formation had minimal effect on pharmacokinetic parameters, a phase I study reported that 2 (5%) of 39 patients who developed persistent positive antibodies also experienced infusion reactions as well as markedly reduced brentuximab vedotin exposure.[29] At present, the significance of antibodies against brentuximab vedotin on safety and efficacy is unknown; therefore, routine screening of patients for brentuximab vedotin antibody formation is not recommended.

Table 2. Dosage Modifications for Brentuximab Vedotin–Related Toxicities[22]

Graded Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Peripheral neuropathy	No dosage adjustment	Withhold dose until neuropathy improves to grade 1 or baseline; restart at 1.2 mg/kg	Withhold dose until neuropathy improves to grade 1 or baseline; restart at 1.2 mg/kg	Discontinue drug
Neutropenia	No dosage adjustment	No dosage adjustment	Withhold dose until neutropenia improves to baseline or grade 2 or less; restart at 1.8 mg/kg with growth factor support	Withhold dose until neutropenia improves to baseline or grade 2 or less; restart at 1.8 mg/kg with growth factor support. If grade 4 neutropenia recurs despite growth factor support, restart at 1.2 mg/kg or consider permanently discontinuing the drug
Serious ungraded toxicity				
Infusion reactions	Interrupt infusion if infusion reaction occurs, treat patient symptomatically Premedicate with acetaminophen, antihistamine, and corticosteroid in patients with previous infusion reactions Permanently discontinue the drug in patients who experience anaphylaxis			
Stevens-Johnson syndrome	Discontinue drug; provide appropriate therapy for Stevens-Johnson syndrome			
PML	Withhold dose if PML is suspected Permanently discontinue drug if PML diagnosis is confirmed			

PML = progressive multifocal leukoencephalopathy.

Contraindications

A phase I study is evaluating the safety of frontline brentuximab vedotin in combination with ABVD or AVD in patients with newly diagnosed, advanced-stage HL.[34, 35] Interim results showed that a greater percentage of patients in the brentuximab vedotin plus ABVD group (at least 44%) experienced noninfectious pulmonary toxicity compared with historical patients receiving bleomycin regimens without brentuximab vedotin (10–25%). Furthermore, pulmonary toxicity, dyspnea, and interstitial lung disease that could not be differentiated from bleomycin toxicity and was confirmed by radiologic evidence led to bleomycin discontinuation in 11 (44%) of 25 patients, with two of these events resulting in death. Of these 11 patients, 7 (64%) continued treatment with AVD and brentuximab vedotin. Other than cough and dyspnea, no serious pulmonary toxicities were observed in patients treated with AVD and brentuximab vedotin.[34, 44] As a result of these preliminary data, the FDA required that a contraindication warning against the use of brentuximab vedotin with bleomycin be added to the product labeling.[44]

Drug Interactions

Data suggest that MMAE is a substrate and an inhibitor of CYP3A4 and CYP3A5.[22, 45] A phase I, open-label study was conducted to determine drug-drug interactions with brentuximab vedotin.[22, 45] A single dose of brentuximab vedotin 1.2 mg/kg was administered with oral ketoconazole 400 mg, and a single dose of brentuximab vedotin 1.8 mg/kg was administered with oral rifampin 600 mg or intravenous midazolam 1 mg. A 34% increased exposure and a 46% decreased exposure to MMAE was reported when ketoconazole (potent CYP3A4 inhibitor) and rifampin (potent CYP3A4 inducer), respectively, were coadministered with brentuximab vedotin. However, the pharmacokinetic parameters for midazolam, which is a sensitive CYP3A4 substrate, were not altered when coadministered with brentuximab vedotin. Because of these data, carefully monitoring for brentuximab vedotin–associated adverse events when the drug is concomitantly given with strong CYP450 inhibitors and inducers is warranted. Interactions with CYP3A4 substrates are not anticipated at significant clinical concentrations.[24] Moreover, bren-

tuximab vedotin is not expected to alter the exposure to drugs that are metabolized by CYP3A4 enzymes.[22]

Dosing and Administration

The maximum tolerated dose of brentuximab vedotin was determined in a phase I, open-label, dose-escalation trial.[28] Patients received brentuximab vedotin as a 2-hour intravenous infusion at doses ranging from 0.1–3.6 mg/kg every 3 weeks (cycle 1). The dose of brentuximab vedotin was based on actual body weight, with a ceiling dose calculated by using a weight of 100 kg for those patients who exceeded 100 kg. Dose-limiting toxicities of grade 3 or higher (nonhematologic events, neutropenia, or febrile neutropenia) or grade 4 thrombocytopenia were evaluated during cycle 1. Results of this trial showed that 1.8 mg/kg was the highest dose acceptable for limiting toxicities and led the FDA to approve brentuximab vedotin at a dosing regimen of 1.8 mg/kg (100 kg maximum weight or 180 mg/dose) as an intravenous infusion over 30 minutes every 3 weeks.[22, 28] Dose delays or adjustments are recommended if patients experience various toxicities during treatment with brentuximab vedotin (Table 2).[22] Treatment duration ranged from 2–12 doses for the six patients in the 1.8-mg/kg cohort who achieved complete response or partial remission.[28]

In phase II trials, treatment courses ranged from 1–16 cycles, with the median number of cycles administered being 7–9.[20, 21] Product labeling states that the treatment course for brentuximab vedotin is a maximum of 16 cycles or until disease progression or the development of unacceptable toxicities.[22] An extension study evaluating prolonged treatment courses (> 16 cycles) in 15 patients with relapsed or refractory HL or sALCL is ongoing.[46] Early results reported that prolonged therapy (median 19 cycles, range 17–29) is safe and maintains clinical responses.

Availability and Storage

Brentuximab vedotin is supplied as a preservative-free, single-dose vial containing 50 mg of white to off-white, lyophilized powder. Before reconstitution, the vial should be stored in the refrigerator (2–8°C or 36–46°F) and must be protected from light.[22] Once reconstituted, the solution in the vial should be stored in the refrigerator, for up to 24 hours.[22] Product labeling recommends that after further dilution, the brentuximab vedotin infusion should be administered immediately; however, if properly stored under refrigeration, it can still be given if used within 24 hours.[22]

Preparation

Before administration, brentuximab vedotin must be reconstituted and further diluted. The 50-mg powder vial must be reconstituted with 10.5 ml of sterile water for injection USP (final concentration 5 mg/ml) and then further diluted in a compatible solution (i.e., 0.9% sodium chloride, 5% dextrose in water, or lactated Ringer's solution) of at least 100 ml. The final product should be prepared to achieve a final concentration ranging from 0.4–1.8 mg/ml.[22]

Economic Considerations

Given that brentuximab vedotin has only recently entered the U.S. market, prescriber uptake and cost impact for patients are unclear. At a wholesale acquisition cost of $4500/50-mg vial, a single dose (based on 1.8 mg/kg for a 70-kg patient) would cost approximately $13,500.[47] Results of clinical trials have reported that the median treatment duration for brentuximab vedotin is approximately 7–9 cycles.[20, 21] Based on these data, the total cost for a course of therapy would range from $94,500–121,500. Moreover, product labeling states that brentuximab vedotin may be administered for a maximum of 16 cycles,[24] which translates into a drug treatment cost exceeding $200,000.

Seattle Genetics, Inc. (the manufacturer of brentuximab vedotin) has established a broad assistance program (SeaGen Secure Patient Assistance Program) for patients who are prescribed brentuximab vedotin and for health care providers who care for these patients.[48] The program consists of services to help with patient assistance and reimbursement support, benefits verification, prior authorization assistance, coinsurance aid, claims tracking, appeal assistance and tracking, billing and coding, and general payer and policy research. For patients to receive brentuximab vedotin at no cost, they must lack prescription coverage, have a gross family income of $125,000 or lower, carry a diagnosis consistent with the FDA-approved indications, and be a permanent resident of the United States or its territories.[49]

Place in Therapy

Clinical trials evaluating brentuximab vedotin have reported response rates (ORR and complete response rate) in patients with relapsed or refractory HL or sALCL.[20, 21] Moreover, the NCCN HL panel has recently included brentuximab vedotin as an option for patients with progressive disease after ASCT or at least two prior chemotherapy regimens for all patients regardless of their eligibility for transplantation. Likewise, the NCCN non-Hodgkin lymphoma panel included brentuximab vedotin as a second-line chemotherapy option before transplantation for patients with sALCL.[1, 2]

Many unanswered questions remain about brentuximab vedotin's optimal placement for the treatment of HL and sALCL. To our knowledge, no published prospective data exist using survival as a primary end point with brentuximab vedotin use; however, this outcome is being evaluated in the ongoing phase III AETHERA study, which has an estimated study completion date of April 2016.[31] More studies are needed to address the importance of achieving complete response with conventional chemotherapy before transplantation in the treatment of relapsed HL in the setting of brenxutimab vedotin availability. The question of whether brentuximab vedotin, in combination with chemotherapy to enhance complete response, may actually increase the number of patients eligible for transplantation also merits consideration. Further research evaluating brentuximab vedotin as initial therapy either alone or in combination with chemotherapy for HL and sALCL is also needed. Finally, the safety profile of brentuximab vedotin when used in patients who develop positive antibodies, for longer courses of therapy, or in combination with chemotherapy, needs to be addressed. Several clinical studies are under way to help answer these questions and further define brentuximab vedotin's optimal placement in the treatment algorithms for HL and sALCL as well as a number of other CD30-positive diseases and populations.

As survival data are minimal, the associated drug cost is high, and reimbursement when used off-label is unknown, brentuximab vedotin therapy should be limited to its FDA indications. However, clinicians need to be aware that a number of clinical trials evaluating brentuximab vedotin in various malignancies and diseases are ongoing and should consider enrolling patients who may be candidates for off-label uses into these clinical trials.

Conclusion

Brentuximab vedotin, a CD30-directed ADC, is the first agent approved for the treatment of HL in nearly three decades and the first agent specifically indicated to treat sALCL. Two open-label, phase II clinical trials have established its efficacy in patients with refractory or relapsed HL and sALCL. In these trials, brentuximab vedotin 1.8 mg/kg given every 3 weeks for up to 52 weeks demonstrated improved response rates in those with HL or sALCL (ORR 75% and 86% and complete response 34% and 57%, respectively). Although not compared directly in clinical trials, these response rates are higher than those for many current treatments of refractory or relapsed HL and sALCL. Adverse effects associated with brentuximab vedotin are considered manageable and are often grade 1 or 2 in severity; however, several serious adverse effects (e.g., neutropenia, peripheral sensory neuropathy, tumor lysis syndrome, Stevens-Johnson syndrome, and PML resulting in death) have been reported with its use. Results of ongoing trials will determine if brentuximab vedotin has a survival benefit when compared directly with standard treatments and if brentuximab vedotin is safe and efficacious when given earlier in the disease process or when used in combination with other chemotherapy for the treatment of HL and sALCL or other CD30-positive malignancies.

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