2010

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ORIGINAL ARTICLE

Brentuximab Vedotin (SGN-35) for Relapsed CD30-Positive Lymphomas

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ABSTRACT

BACKGROUND

Hodgkin's lymphoma and anaplastic large-cell lymphoma are the two most common tumors expressing CD30. Previous attempts to target the CD30 antigen with monoclonal-based therapies have shown minimal activity. To enhance the antitumor activity of CD30-directed therapy, the antitubulin agent monomethyl auristatin E (MMAE) was attached to a CD30-specific monoclonal antibody by an enzyme-cleavable linker, producing the antibody–drug conjugate brentuximab vedotin (SGN-35).

METHODS

In this phase 1, open-label, multicenter dose-escalation study, we administered brentuximab vedotin (at a dose of 0.1 to 3.6 mg per kilogram of body weight) every 3 weeks to 45 patients with relapsed or refractory CD30-positive hematologic cancers, primarily Hodgkin's lymphoma and anaplastic large-cell lymphoma. Patients had received a median of three previous chemotherapy regimens (range, one to seven), and 73% had undergone autologous stem-cell transplantation.

RESULTS

The maximum tolerated dose was 1.8 mg per kilogram, administered every 3 weeks. Objective responses, including 11 complete remissions, were observed in 17 patients. Of 12 patients who received the 1.8-mg-per-kilogram dose, 6 (50%) had an objective response. The median duration of response was at least 9.7 months. Tumor regression was observed in 36 of 42 patients who could be evaluated (86%). The most common adverse events were fatigue, pyrexia, diarrhea, nausea, neutropenia, and peripheral neuropathy.

CONCLUSIONS

Brentuximab vedotin induced durable objective responses and resulted in tumor regression for most patients with relapsed or refractory CD30-positive lymphomas in this phase 1 study. Treatment was associated primarily with grade 1 or 2 (mild-to-moderate) toxic effects. (Funded by Seattle Genetics; ClinicalTrials.gov number, NCT00430846.)

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N Engl J Med 2010;363:1812-21.

Approximately 15 to 30% of patients with Hodgkin's lymphoma do not have a long-term remission with conventional therapy,[1] resulting in an estimated 1300 deaths annually in the United States alone.[2] Autologous hematopoietic stem-cell transplantation (ASCT) represents a potentially curative treatment for some patients with recurrent or progressive Hodgkin's lymphoma after failure of initial combination chemotherapy. Unfortunately, ASCT is only effective in approximately 50% of such patients.[3,4] Among those who have a relapse after ASCT, overall survival is 55% at 2 years and 32% at 5 years.[5] Because the incidence of Hodgkin's lymphoma peaks during young adulthood, these premature deaths have a substantial social impact.[6]

In Hodgkin's lymphoma, malignant Hodgkin's Reed–Sternberg (HRS) cells typically represent a small fraction (0.1 to 10%) of the nodal infiltrate.[7] HRS cells reside among reactive inflammatory cells, consisting of a dense infiltrate of T cells, histiocytes, eosinophils, and plasma cells. HRS cells appear to attract these cells to the microenvironment by secreting type 2 helper T chemokines and cytokines, such as thymus and activation-regulated chemokine (TARC, or CCL17). In turn, the immune cells appear to support the HRS cells by secreting survival factors.[8,9] Conceivably, the ablation of HRS cells could prompt nodal regression and potentially result in prolonged clinical remission.

CD30 is expressed on the surface of HRS cells and cells in anaplastic large-cell lymphomas (ALCLs), embryonal carcinomas, and select subtypes of B-cell derived, non-Hodgkin's lymphomas and mature T-cell lymphomas.[10-12] Because normal expression of CD30 is highly restricted to a relatively small population of activated B cells and T cells and a small portion of eosinophils,[10-12] the deletion of CD30-expressing cells could represent a novel and selective treatment strategy. Although preclinical data suggested that unconjugated anti–CD30 antibodies might have therapeutic value,[13] minimal clinical activity has been reported. Objective responses were observed in 6% of patients with Hodgkin's lymphoma who were treated with MDX-060[14] and in none of those treated with SGN-30 (monoclonal antibody cAC10).[15]

To enhance antitumor activity, the antitubulin agent monomethyl auristatin E (MMAE) was attached to the CD30-specific monoclonal antibody cAC10 by an enzyme-cleavable dipeptide linker,[16] producing the antibody–drug conjugate brentuximab vedotin (SGN-35, Seattle Genetics).[17] After binding CD30, the antibody–drug conjugate is rapidly internalized and is transported to lysosomes, where the peptide linker is selectively cleaved. MMAE is then released into the cell, binds tubulin, and prompts arrest of the cell cycle between the gap 2 phase and mitosis (G2/M) and cell apoptosis (Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). In vitro, the drug was found to be potent and selective against CD30-positive tumor-cell lines, and activity was observed in models of Hodgkin's lymphoma and ALCL in mice with severe combined immunodeficiency.[18-20]

To assess the safety and clinical activity of brentuximab vedotin, we treated patients with relapsed or refractory CD30-positive hematologic cancers in a phase 1, open-label, dose-escalation trial. Furthermore, because serum levels of TARC have been shown to correlate with disease activity in patients with Hodgkin's lymphoma,[21,22] we evaluated serum levels of TARC and various cytokines in patients in the expansion phase of the study.

METHODS

PATIENTS

From November 2006 through July 2009, we collected data at four study centers in the United States. Patients had relapsed or refractory, histologically confirmed CD30-positive hematologic cancers. Patients with Hodgkin's lymphoma had received systemic chemotherapy either as induction therapy for advanced-stage disease or salvage therapy after initial radiotherapy for early-stage disease and had previously undergone ASCT unless they were ineligible or declined treatment. Patients with other CD30-positive cancers, such as systemic ALCL, had already had a first remission or had disease refractory to front-line chemotherapy.

To be eligible for study enrollment, patients needed to be at least 18 years of age, have a measurable tumor of at least 10 mm in diameter, and have an Eastern Cooperative Oncology Group performance status of 2 or less (on a scale of 0 to 5, with higher scores indicating more severe disability).[23] Patients were excluded if they had undergone allogeneic stem-cell transplantation.

STUDY DESIGN

The primary objectives of the study were to define the safety profile of brentuximab vedotin and to determine the maximum tolerated dose (the highest dose that would not produce unacceptable toxic effects). Secondary objectives were to determine pharmacokinetic measures for the antibody–drug conjugate and MMAE, evaluate immunogenicity, and assess antitumor response. Exploratory analysis of cytokines and chemokines was limited to patients in the expansion phase of the study.

Brentuximab vedotin was administered intravenously at doses of 0.1 to 3.6 mg per kilogram of body weight every 3 weeks (one cycle); premedication was not required. The study used a traditional dose-escalation design, followed by a cohort expansion phase. Dose-limiting toxic effects, which were assessed during the 21-day observation period of cycle 1, included related nonhematologic events of grade 3 or higher, clinically significant grade 3 or 4 neutropenia or febrile neutropenia, and grade 4 thrombocytopenia. (Additional details about dose-limiting toxic effects are provided in Table 1 in the Supplementary Appendix.) If 1 of the first 3 patients had a dose-limiting toxic effect, the cohort was expanded to 6 patients. If at least 2 of 6 patients within a cohort had a dose-limiting toxic effect, the maximum tolerated dose was considered to have been exceeded. After the maximum tolerated dose was exceeded, additional patients were to be enrolled at the preceding dose for a total of 12 patients; an additional cohort at a lower dose level also could be expanded.

Response was assessed every 6 weeks. Patients with complete remission, partial remission, or stable disease with protocol-defined clinical benefit (improved performance status, decreased analgesic consumption, or decreased disease volume) could continue therapy. Study treatment was discontinued on confirmation of disease progression. After treatment discontinuation, patients were monitored for a minimum of 30 days after the last dose of brentuximab vedotin or until they received another treatment for lymphoma.

STUDY ASSESSMENTS

Safety monitoring included the assessment of adverse events, dose-limiting toxic effects, and clinical laboratory values. Adverse events were summarized according to terms used in the *Medical Dictionary for Regulatory Activities,* version 11.1, and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.[24]

Serum concentrations of brentuximab vedotin were assessed with the use of a validated enzyme-linked immunosorbent assay (ELISA). Derived pharmacokinetic measures were estimated by means of noncompartmental methods (WinNonlin, Pharsight). Immunogenicity to brentuximab vedotin was assessed before each dose by means of a validated ELISA.

The best clinical response was determined by the academic investigators. The definition of a best clinical response was based on the 2007 Revised Response Criteria for Malignant Lymphoma.[25] A complete response was defined as the disappearance of all evidence of disease, a partial response as a decrease of at least 50% in the sum of the product of diameters of measurable target lesions and no new lesions, stable disease as the lack of a complete or partial response and no occurrence of progressive disease, and progressive disease as any new lesion or an increase of at least 50% in the sum of the product of diameters of previously involved sites.[25] An independent review facility (RadPharm) retrospectively evaluated the radiographic scans.

Cytokines and chemokines, including tumor necrosis factor α (TNF-α), interleukins (1β, 2, 6, and 8), granulocyte–macrophage colony-stimulating factor, interferon-gamma, and TARC were evaluated for patients in the expansion phase of the study (six patients each in the 1.8-mg cohort and the 2.7-mg cohort). Serum samples were drawn at baseline, before and 4 hours after each dose of the study drug, and at the end of treatment. TARC was measured by means of ELISA (R&D Systems), and cytokines were measured by means of electrochemiluminescence assays (Meso Scale Diagnostics). These assays were performed by an independent laboratory after study completion.

STUDY OVERSIGHT

The study was sponsored by Seattle Genetics. The academic investigators and the sponsor were jointly responsible for the study design. The academic investigators collected the data, and the sponsor verified the accuracy of the data. One of the academic authors and a representative of the sponsor wrote the first draft of the manuscript, which was finalized and approved by all authors. Representatives of the sponsor conducted and verified

the statistical analyses and provided assistance in the preparation of the manuscript, including the services of a paid consultant who assisted in the editorial and submission process. All authors had full access to the data, contributed to the interpretation, and vouch for the completeness and accuracy of the results and the adherence of the reported results to the final protocol. The protocol was approved by the institutional review board at each study site, and all patients provided written informed consent before study-specific procedures began. The protocol and statistical analysis plan are available at NEJM.org.

RESULTS

PATIENTS

Of the 45 patients who were treated, 42 had Hodgkin's lymphoma, 2 had systemic ALCL, and 1 had CD30-positive angioimmunoblastic T-cell lymphoma (Table 1). The median age of the patients was 36 years (range, 20 to 87). Patients had undergone a median of 3 previous chemotherapy regimens (range, 1 to 7), and 33 patients (73%) had undergone previous autologous stem-cell transplantation.

SAFETY PROFILE AND MAXIMUM TOLERATED DOSE

A dose-limiting toxic effect (grade 4 thrombocytopenia) occurred in 1 of 6 patients who received a dose of 1.8 mg per kilogram; unrelated grade 3 acute renal failure occurred in 1 of 6 patients who received a dose of 2.7 mg per kilogram. In the single patient who received a dose of 3.6 mg per kilogram, febrile neutropenia and presumed sepsis developed, which both contributed to death 14 days after the first dose. Subsequently, the 1.8-mg and 2.7-mg cohorts were both expanded to include 12 patients each. At the 2.7-mg dose, 2 additional patients had three dose-limiting toxic effects (grade 3 hyperglycemia in the first patient and grade 3 unrelated prostatitis and febrile neutropenia in the second patient) for a total of 3 of 12 patients with dose-limiting toxic effects at this dose level. On the basis of these observations, a dose of 2.7 mg per kilogram was associated with unacceptable toxic effects, and 1.8 mg per kilogram was considered the highest dose that did not cause unacceptable adverse effects.

The most common adverse events, typically grade 1 or 2 in severity, were fatigue (16 patients, 36%), pyrexia (15 patients, 33%), and diarrhea, nausea, neutropenia, and peripheral neuropathy (10 patients, 22% each) (Table 2). A total of 27 serious adverse events occurred in 14 patients (31%) during the study (Table 2 in the Supplementary Appendix); of these events, 9 (33%) were

Table 1. Demographic and Clinical Characteristics of the 45 Patients.

Characteristic	Value
Age	
Median — yr	36
Range — yr	20–87
≤65 yr — no. (%)	41 (91)
Sex — no. (%)	
Male	28 (62)
Female	17 (38)
ECOG status — no. (%)*	
0	28 (62)
1	14 (31)
2	3 (7)
Diagnosis — no. (%)	
Hodgkin's lymphoma	42 (93)
Anaplastic large-cell lymphoma (systemic)	2 (4)†
Angioimmunoblastic T-cell lymphoma	1 (2)
Time since initial diagnosis — mo	
Median	39
Range	8–253
Stage at initial diagnosis — no. (%)	
I	1 (2)
II	21 (47)
III	12 (27)
IV	11 (24)
Tumor burden (sum of product of diameters) — cm^2	
Median	22.24
Range	2.83–179.78
Patients with fever, night sweats, or weight loss — no. (%)	16 (36)
Previous therapy	
Systemic chemotherapy — no. (%)	45 (100)
Median no. of therapies	3
Range	1–7
Autologous stem-cell transplantation — no. (%)	33 (73)
Radiotherapy — no. (%)	27 (60)
Cancer-related surgery — no. (%)	14 (31)

* Eastern Cooperative Oncology Group (ECOG) performance scores range from 0 (normal activity) to 5 (death), with higher scores indicating more severe disability.

† Both patients with anaplastic large-cell lymphoma tested positive for anaplastic lymphoma kinase (ALK) protein.

Table 2. Common Adverse Events, According to Dose of Brentuximab Vedotin.*

Adverse Event	<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)				All Doses (N=45)
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3	Grade 4	
	number of patients															*no. (%)*
Fatigue	4	1	0	1	0	2	2	0	5	1	0	0	0	0	0	16 (36)
Pyrexia	4	2	0	0	0	3	0	0	2	1	2§	0	0	0	1	15 (33)
Diarrhea	6	0	0	1	0	1	0	0	0	1	0	0	1	0	0	10 (22)
Nausea	2	1	0	0	0	4	0	0	1	1	0	0	1	0	0	10 (22)
Neutropenia	0	0	0	0	1	0	3	1	0	3	2	0	0	0	0	10 (22)
Peripheral neuropathy	1	0	0	0	1	2	2	0	4	0	0	0	0	0	0	10 (22)
Headache	2	0	0	1	0	3	0	0	3	0	0	0	0	0	0	9 (20)
Vomiting	5	0	0	0	0	2	0	0	0	1	0	0	0	1	0	9 (20)
Back pain	1	1	0	1	0	2	0	1	0	2	0	0	0	0	0	8 (18)
Anemia	0	3	1§	0	0	0	0	0	0	0	2	0	0	1	0	7 (16)
Alopecia	0	0	0	0	0	1	0	0	5	0	0	0	0	0	0	6 (13)
Constipation	1	0	0	0	0	1	0	0	4	0	0	0	0	0	0	6 (13)
Cough	2§	1	0	0	0	2	1	0	0	0	0	0	0	0	0	6 (13)
Night sweats	1	0	0	0	0	2	0	0	3	0	0	0	0	0	0	6 (13)
Pain in limb	1	0	0	0	0	1	0	1	3	0	0	0	0	0	0	6 (13)
Upper respiratory tract infection	2	0	0	2	0	0	1	0	1	0	0	0	0	0	0	6 (13)
Abdominal pain	0	0	0	0	0	2	0	0	2	0	1	0	0	0	0	5 (11)
Arthralgia	0	1	0	0	0	1	0	0	0	3	0	0	0	0	0	5 (11)
Insomnia	2	0	0	0	0	0	0	0	3	0	0	0	0	0	0	5 (11)
Tachycardia	2	1	0	1	0	0	0	0	0	0	0	0	0	0	1	5 (11)

* Listed are adverse events that were reported in at least 10% of patients, with the maximum grade for each patient. Adverse events were collected for at least 30 days after the last dose of brentuximab vedotin and were summarized according to terms used in the *Medical Dictionary for Regulatory Activities*, version 11.1, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

† No grade 4 common adverse events were reported for this dose.

‡ No grade 3 or 4 common adverse events were reported for this dose.

§ Serious adverse events were reported by the investigator for 2 patients with grade 3 pyrexia, 1 patient with grade 3 anemia, and 1 patient with grade 1 cough.

Table 3. Best Clinical Response in 45 Patients.*

Response	Dose (mg/kg)								
	0.1 (N=3)	0.2 (N=4)	0.4 (N=3)	0.6 (N=3)	0.8 (N=3)	1.2 (N=4)	1.8 (N=12)	2.7 (N=12)	3.6 (N=1)
Complete remission	0	0	0	0	0	1†	4	6†	0
Partial remission	0	0	0	2	0	1	2	1	0
Stable disease	2	0	2	1	2	2	5	5	0
Progressive disease	1	4‡	1	0	1	0	1	0	0
Could not be evaluated	0	0	0	0	0	0	0	0	1§

* The best clinical response was determined by investigators on the basis of the 2007 Revised Response Criteria for Malignant Lymphoma.[25]
† Both patients with systemic anaplastic large-cell lymphoma (one each in the 1.2-mg cohort and the 2.7-mg cohort) had a complete remission.
‡ One patient with angioimmunoblastic T-cell lymphoma (in the 0.2-mg cohort) had a best clinical response of progressive disease.
§ Postbaseline disease assessment was not available for the patient who received a dose of 3.6 mg per kilogram.

considered by the investigators to be related to the study drug. The most commonly observed laboratory abnormalities of grade 3 or higher are provided in Table 3 in the Supplementary Appendix.

Dose delays because of adverse events occurred in 16 patients (36%). A total of 12 patients (27%) had adverse events other than progression that led to treatment withdrawal, including 2 patients each with fatigue and thrombocytopenia. One patient discontinued treatment after having an anaphylactic reaction during administration of the second 1.8-mg dose. The administration of a dose was interrupted in another patient in the same cohort because of an infusion-related reaction; after receiving treatment for the reaction, the patient recovered for approximately 2 hours and then the infusion was restarted without further incident.

Peripheral neuropathy and associated adverse events related to neuropathy were reported in 16 patients (36%), 13 of whom were treated at the 1.8-mg or 2.7-mg dose. Patients with peripheral neuropathy typically presented with grade 1 or 2 sensory findings, such as numbness or tingling in the hands or feet, and the median time to onset was 9 weeks (range, 3 to 24). Resolution of peripheral neuropathy was noted in 10 of 16 patients (63%) at the last safety assessment; 3 patients had ongoing asymptomatic grade 1 findings, and 3 patients had persistent grade 2 symptoms that were considered to be clinically significant. Three patients discontinued treatment because of peripheral neuropathy (grade 2 peripheral neuropathy, grade 2 peripheral sensory neuropathy, and grade 3 peripheral sensorimotor neuropathy). Of note, the only grade 3 event, which was observed in a patient in the 2.7-mg cohort, returned to grade 1 after approximately 4 months.

All patients tested negative for antitherapeutic antibody at baseline. Of the 40 patients who were tested, 2 (5%) were found to have a low titer of antitherapeutic antibody during the study; both of these patients had a best clinical response of stable disease. One patient in the 0.1-mg cohort tested positive for antitherapeutic antibody from cycle 6 through cycle 16. The other patient, who was in the 1.2-mg cohort, tested positive after four cycles of the study drug. Because of the low incidence of detection of antitherapeutic antibody, no conclusions can be drawn regarding the potential effect of the presence of antitherapeutic antibody on safety or activity of the study drug.

PHARMACOKINETICS AND PHARMACODYNAMICS

Increases in exposure to the antibody–drug conjugate and free MMAE were approximately proportional to dose. The median time to maximum concentration occurred immediately after infusion for the antibody–drug conjugate and approximately 2 to 3 days after infusion for MMAE. Steady-state pharmacokinetics for both the antibody–drug conjugate and MMAE occurred by approximately 21 days, consistent with the half-life estimates of 4 to 6 days and 3 to 4 days, respectively. Concentration–time curves and pharmacokinetic measures are provided in the Supplementary Appendix (Fig. 2 and Table 4, respectively).

Table 4. Previous Therapy, Disease Characteristics, and Treatment Response in 11 Patients with Complete Remission and 6 Patients with Partial Remission.*

Response and Diagnosis	Previous Therapy†	Duration of Response to Most Recent Previous Therapy
		mo
Complete remission		
Anaplastic large-cell lymphoma	CHOP, radiotherapy, ICE, cyclophosphamide–etoposide, ASCT	15 (partial response)
Hodgkin's lymphoma	ABVD, radiotherapy, ICE, ASCT	8 (complete response)
Hodgkin's lymphoma	ABVD, ICE, ASCT	NA (progressive disease)
Hodgkin's lymphoma	ABVD, radiotherapy, ICE, ASCT	10 (complete response)
Hodgkin's lymphoma	ABVD, radiotherapy, ABVD, radiotherapy, radiotherapy, R-ESHAP, GND, ifosfamide–etoposide, GND	24 (complete response)
Hodgkin's lymphoma	ABVD, ASCT, interleukin-2, carboplatin–etoposide–prednisone	1 (partial response)
Anaplastic large-cell lymphoma	CHOP	3.5 (complete response)
Hodgkin's lymphoma	ABVD, doxorubicin–bleomycin–dacarbazine, ICE, ASCT	12 (partial response)
Hodgkin's lymphoma	ABVD, radiotherapy, ICE, ASCT, MGCD-0103	3 (stable disease)
Hodgkin's lymphoma	ABVD, ICE, ASCT, gemcitabine–vinorelbine, MGCD-0103	12 (complete response)
Hodgkin's lymphoma	ABVD, radiotherapy, ICE, ASCT, GDP, radiotherapy, hyper-CVAD, methotrexate–cytarabine, rituximab	NA (progressive disease)
Partial remission		
Hodgkin's lymphoma	ABVD	17 (partial response)
Hodgkin's lymphoma	BEAM, ABVD, IVE, ASCT, radiotherapy, ESHAP, radiotherapy, gemcitabine	28 (complete response)
Hodgkin's lymphoma	ABVD, ESHAP, gemcitabine–cisplatin–dexamethasone, cyclophosphamide–etoposide, ASCT	7 (complete response)
Hodgkin's lymphoma	ABVD, radiotherapy, ICE, cisplatin–gemcitabine, ASCT	2 (complete response)
Hodgkin's lymphoma	ABVD, radiotherapy, ESHAP, radiotherapy, ASCT, radiotherapy	17 (complete response)
Hodgkin's lymphoma	Stanford V, radiotherapy, ESHAP, IGEV, MGCD-0103	NA (progressive disease)

* ABVD denotes doxorubicin, bleomycin, vinblastine, and dacarbazine, ASCT autologous stem-cell transplantation, BEAM carmustine, etoposide, cytarabine, and melphalan, CHOP cyclophosphamide, doxorubicin, vincristine, and prednisone, ESHAP etoposide, methylprednisolone, cytarabine, and cisplatin, GDP gemcitabine, dexamethasone, and cisplatin, GND gemcitabine, vinorelbine, and doxorubicin, hyper-CVAD cyclophosphamide, vincristine, doxorubicin, dexamethasone, cytarabine, and methotrexate followed by methotrexate, leucovorin, and cytarabine, ICE ifosfamide, carboplatin, and etoposide, IGEV ifosfamide, gemcitabine, vinorelbine, and prednisone, IVE ifosfamide, etoposide, and epirubicin, MGCD-0103 oral histone deacetylase inhibitor, NA not applicable, R-ESHAP rituximab and ESHAP, and Stanford V bleomycin, doxorubicin, etoposide, mechlorethamine, prednisone, vinblastine, and vincristine.
† Previous therapies are listed in sequential order of administration.
‡ Tumor burden was measured as the sum of the products of bidimensional measurements of target lesions.
§ Each dose could be delayed up to 2 weeks to allow for resolution of toxic effects of grade 2 or higher.

Decreases in serum TARC levels were observed in all 12 patients for whom data were collected (Fig. 3 in the Supplementary Appendix). Post-baseline decreases in levels of interleukin-6 and TNF-α also were noted in 10 of 12 patients each (data not shown).

ANTITUMOR RESPONSE

Objective responses were noted in 17 patients, including 11 complete remissions (Table 3). Data on previous therapies, baseline disease characteristics, and treatment response for all patients who had an objective response are provided in Table 4. For patients who received the maximum tolerated dose (1.8 mg per kilogram), the objective response rate was 50% (6 of 12 patients). Complete remission occurred in patients with bulky disease as well as those with widespread nodal disease (Fig. 4 in the Supplementary Appendix). Of the 17 patients with an objective response, 15 (88%)

Site of Measurable Tumors at Baseline	Disease Burden at Baseline‡	Dose of Brentuximab Vedotin	Total Doses	Duration of Treatment§	Time to First Objective Response	Duration of Response
	cm^2	mg/kg	no.	mo		
Nodal	9.07	1.2	14	11.3	1.1	17.3
Lung, pelvis, other (not specified)	10.58	1.8	5	4.8	1.4	16.0+
Nodal	6.15	1.8	11	9.7	2.6	9.7
Nodal	40.48	1.8	12	9.7	2.7	19.5+
Nodal	2.83	1.8	6	4.6	1.2	13.8+
Nodal	9.96	2.7	7	6.3	6.3	13.3+
Nodal	9.00	2.7	3	2.5	1.2	5.0
Nodal	9.22	2.7	6	4.4	1.7	1.4+
Nodal	69.44	2.7	8	6.2	1.2	3.4
Nodal	3.52	2.7	3	3.0	1.7	13.3+
Nodal	52.98	2.7	4	4.0	1.4	9.0
Pelvis	8.92	0.6	2	2.0	1.2	0.6
Nodal	112.06	0.6	8	6.2	1.4	9.6
Nodal	7.40	1.2	5	4.0	3.3	1.1+
Lung	24.78	1.8	8	6.3	1.2	5.1
Nodal	22.24	1.8	2	1.8	1.7	14.6+
Nodal	27.18	2.7	10	9.5	2.7	11.5+

had an initial response within four treatment cycles (2.8 months). In addition, 19 of 44 patients who could be evaluated (43%) had stable disease.

Tumor regression, as observed on computed tomography (CT), was reported for 36 of 42 patients who could be evaluated (86%) (Fig. 5 in the Supplementary Appendix). Of 16 patients with disease-related symptoms at baseline, 13 (81%) had resolution of symptoms during treatment, regardless of response status.

An independent, retrospective assessment of CT and positron-emission tomographic scans for the 45 patients showed response rates similar to those reported by investigators, with responses reported for 18 patients (40%), as compared with 17 patients (38%) reported by investigators. For the 12 patients who received the 1.8-mg dose, independent reviewers reported a response in 8 patients (67%), as compared with 6 patients (50%) reported by investigators. Among 41 patients for whom evaluations by both investigators and independent reviewers were available, there was a significant correlation between the findings of the independent reviewers and those of the investigators with respect to the maximum reduction in target lesions (Pearson correlation, 0.719; 95% confidence interval, 0.528 to 0.841).

The Kaplan–Meier estimate for the duration of objective response was 17.3 months for the 17 patients with an objective response (range, 0.6 to >19.5) (Fig. 6 in the Supplementary Appendix). The median duration of objective response was at least 9.7 months on the basis of a conservative analysis that assumed progression on the date of data

Table 5. Clinical Activity of Brentuximab Vedotin, as Compared with Unconjugated Antibody SGN-30.*

Variable	SGN-30	Brentuximab Vedotin
All patients		
No. of patients	79	28
Objective response — no. (%)		
Any	7 (9)	15 (54)
Complete remission	2 (3)	11 (39)
Partial remission	5 (6)	4 (14)
Hodgkin's lymphoma		
No. of patients	38	26
Objective response — no. (%)		
Any	0	13 (50)
Complete remission		9 (35)
Partial remission		4 (15)
Anaplastic large-cell lymphoma		
No. of patients	41	2
Objective response — no. (%)		
Any	7 (17)	2 (100)
Complete remission	2 (5)	2 (100)
Partial remission	5 (12)	

* The results for SGN-30, an unconjugated anti-CD30 monoclonal antibody (cAC10) administered at a dose of 6 or 12 mg per kilogram per week, were reported by Forero-Torres et al.[15] Brentuximab vedotin (SGN-35), administered at a dose ranging from 1.2 to 2.7 mg per kilogram every 3 weeks, is a conjugate of cAC10 and antitubulin agent monomethyl auristatin E (MMAE).

censoring (i.e., for patients who discontinued the study for reasons other than documented progression or death). The median progression-free survival was 5.9 months, with a trend toward longer progression-free survival in patients receiving doses of at least 1.2 mg per kilogram (Fig. 7 in the Supplementary Appendix).

DISCUSSION

Tumor regression was observed in the majority of patients who were treated with brentuximab vedotin, which was associated mainly with grade 1 or 2 fatigue, pyrexia, diarrhea, nausea, neutropenia (with one grade 3 event), and peripheral neuropathy at the maximum tolerated dose. Objective responses, including 11 complete remissions, were observed in 17 patients; of 12 patients receiving the maximum tolerated dose, 6 (50%) had an objective response. Lending validity to these results, an independent, retrospective radiographic review corroborated the rate of response and reduction in target lesions. The objective response rate in patients receiving brentuximab vedotin who had undergone previous intensive therapies for Hodgkin's lymphoma and systemic ALCL is particularly striking in comparison with the minimal activity elicited by the same unconjugated anti-CD30 monoclonal antibody (Table 5), suggesting the essential contribution of the selectively delivered cytotoxic agent.

Remissions were durable in this population of patients who had relapsed or refractory disease, with a median duration of at least 9.7 months. Responses that were associated with modest durability have been reported in monotherapy case series evaluating gemcitabine, vinorelbine, or vinblastine.[26-31] Combination regimens (e.g., gemcitabine, vinorelbine, and pegylated liposomal doxorubicin) have shown somewhat higher response rates but have been associated with substantial toxic effects.[32] However, complete remissions are rare in patients with drug-refractory Hodgkin's lymphoma or systemic ALCL, especially in those treated with single agents.

It has been reported that HRS cells secrete cytokines and chemokines, leading to an inflammatory infiltrate that enhances survival of cancer cells.[9] Treatment with brentuximab vedotin led to the resolution of large tumor masses and decreases in levels of chemokines and inflammatory cytokines in patients with Hodgkin's lymphoma, providing clinical data supporting the hypothesis that selective ablation of CD30-positive HRS cells leads to subsequent resolution of the inflammatory infiltrate.

Most adverse events were managed through standard supportive care, and the most common events were typically of grade 1 or 2. The most clinically meaningful adverse events were cumulative, dose-related grade 1 or 2 peripheral neuropathy and associated adverse events related to neuropathy. Since the cytotoxic component of brentuximab vedotin is a potent antitubulin agent, the peripheral neuropathy observed in this study is consistent with a class effect of microtubule inhibitors.[33,34] Resolution of symptoms was observed in the majority of patients during follow-up, although clinically significant grade 2 symptoms persisted in three of six patients at the last safety assessment.

In conclusion, the novel antibody–drug conju-

gate brentuximab vedotin induced durable responses, with moderate adverse effects, in this phase 1 study. Tumor regression was noted in 86% of patients, and tumor-related symptoms were relieved in 81% of those in whom such symptoms were present. Further testing is warranted on the basis of these results.

Supported by Seattle Genetics.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Peter Senter, who led the team effort for developing the brentuximab vedotin drug-conjugate technology, Hong Ren and Yin Yang for statistical guidance, and Roberta Connelly for assistance in the preparation of the manuscript under the sponsorship of Seattle Genetics.

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