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Progressive multifocal leukoencephalopathy associated with brentuximab vedotin therapy: A report of 5 cases from the Southern Network on Adverse Reactions (SONAR) project

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Abstract

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AUTHORSHIP

Contribution: Kenneth R. Carson, Scott D. Newsome, Ellen J. Kim, and Charles L. Bennett did the literature search, study design, data collection, data analysis, data interpretation, and writing of manuscript. Nina Wagner-Johnston, MD, Gloria von Geldern, Craig H. Moskowitz, Alison J. Moskowitz, Alain H. Rook, Pankaj Jalan, Alison W. Loren, Daniel Landsburg, Thomas Coyne, Donald Tsai, Dennis W. Raisch, LeAnn B. Norris, P Brandon Bookstaver, and Oliver Sartor contributed data collection, data interpretation, and edited the manuscript.

Purpose—Brentuximab vedotin (BV) is an anti-CD30 monoclonal antibody-drug conjugate approved in 2011 for treating anaplastic large cell and Hodgkin lymphomas. The product label indicates that three BV-treated patients developed progressive multifocal leukoencephalopathy (PML), a frequently fatal JC-virus induced central nervous system infection. Prior immunosuppressive therapy and compromised immune systems were postulated risk factors. We report 5 patients who developed BV-associated PML, including two immunocompetent patients.

Patients—Case information was obtained from clinicians (four patients) or a Food and Drug Administration database (one patient).

Results—All five patients had lymphoid malignancies. Two patients with cutaneous T-cell lymphomas had not previously received chemotherapy. PML developed after a median of three BV doses (range, 2 to 6) and within a median of 7 weeks following BV initiation (range, 3 to 34 weeks). Presenting findings included aphasia, dysarthria, confusion, hemiparesis, and gait dysfunction; JC virus in cerebrospinal fluid (two patients), or CNS biopsy (three patients); and brain MRI scans with white matter abnormalities (five patients). Four patients died a median of 8 weeks (range, 6 to 16 weeks) after PML diagnosis. The sole survivor developed immune reconstitution inflammatory syndrome.

Conclusion—PML can develop after a few BV doses and within weeks of BV initiation. Clinicians should be aware of this syndrome, particularly when neurologic changes develop following BV initiation. The decision to administer BV to patients with indolent cutaneous lymphomas should be based on consideration of risk-benefit profiles and of alternative options.

INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a rare and often fatal infection of the central nervous system (CNS) that results from reactivation of latent JC polyoma virus (JCV), which typically occurs in immunocompromised patients.[1] In the era of highly active anti-retroviral therapy (HAART), 80% of new PML diagnoses develop among HIV-infected individuals.[2] Prior to the HIV epidemic, however, most PML cases occurred in patients with lymphoproliferative disorders.[3] Among HIV-negative individuals, PML has been most commonly associated with cytotoxic chemotherapy, immune suppressing medications, solid organ and hematopoietic stem cell transplantation.[4–6] PML incidence estimates range from 0.07% in a population based study of persons with hematologic malignancies, 0.5% among fludarabine-treated patients with chronic lymphocytic leukemia, to 3% to 5% among persons diagnosed with AIDS in the post-HAART era.[6] There is a lack of universally accepted treatments for PML outside of trying to help reconstitute the immune system. Immune reconstitution is often achieved through removal of the offending agent that resulted in PML, by stimulating an altered immune system, or by starting antiretroviral therapy in HIV/AIDS cases. Some patients with PML survive following development of an immune reconstitution inflammatory syndrome (IRIS) which is characterized by rapid infiltrates of cytotoxic T-cells.[7] While IRIS development among PML patients can be life-saving, central nervous system inflammation due to IRIS can result in death or permanent neurologic disability.[8]

Most recently, PML has been reported in patients receiving several different immune modulating monoclonal antibodies.[6] These monoclonal antibodies appear to alter normal immune function and/or immune surveillance.[9] Natalizumab, a monoclonal antibody targeted against the alpha-4 integrin, was initially approved for the treatment of multiple sclerosis and Crohn's disease, but was withdrawn from the market in 2005 after three patients developed PML. After implementation of a global risk-management program, natalizumab was reintroduced in 2006.[10] In certain high-risk individuals, natalizumab has been associated with a PML incidence of up to one in 85 exposures.[11] Efalizumab, a monoclonal antibody targeting CD11a, was approved in 2003 for treatment of moderate to severe plaque psoriasis. Marketing of the drug was voluntarily discontinued by the manufacturer in 2009 after three confirmed cases of PML developed in patients who had received several years of efalizumab treatment.[12] Rituximab, an anti-CD20 monoclonal antibody was approved for the treatment of indolent B-cell non-Hodgkin lymphomas in 1997. Over the next nine years, the Food and Drug Administration (FDA) received reports of 10 patients who developed PML following rituximab treatment. In 2009, we reported 57 rituxmab-associated PML cases occurring among patients with autoimmune diseases (five patients) and lymphoproliferative disorders (52 patients).[13] Subsequently, by mid-2012, the FDA had received reports of 511 patients with rituximab-associated PML.

In 2011, the United States FDA granted accelerated approval for brentuximab vedotin (BV), a monoclonal antibody targeting CD30 positive cells, which is conjugated to the cytotoxic agent monomethyl auristatin-E.[14] The approval was for treatment of relapsed or refractory systemic anaplastic large cell lymphoma and classical Hodgkin lymphoma. The initial product label included a warning that one BV-treated patient had developed and subsequently died from PML.[15] In 2012, the manufacturer added a "Black Box" warning to the label indicating that two subsequently reported patients had also developed PML following BV treatment. Long-term clinical follow-up on the three patients was not reported.[16] The warning identified potential contributory risk factors as underlying lymphoproliferative disorders, patients with immune system compromise, and multi-agent chemotherapy treatments. Clinicians were advised that among BV-treated individuals, signs and symptoms of PML, primarily neurologic changes, may develop over the course of several weeks or months.[16]

For all monoclonal antibodies targeting the immune system, vigilant post-marketing surveillance is essential to detect rare disorders like PML.[17] When cases of PML arise, assessment of the risks and benefits of the associated agent for the approved indications is warranted.[11] The FDA noted in January 2012 that three cases of PML were diagnosed among the first 2,000 patients who had received BV, although comprehensive information on presenting findings, prior treatments, PML treatments, and outcome was not provided. In the current study, we summarize the clinical characteristics, interval between BV therapy and onset of disease, response to treatment, pathology/laboratory findings, and long-term outcomes in five patients in whom PML developed after initiating BV treatment. The identification of these five BV-associated PML cases occurred in the first year of marketing of BV.

MATERIALS AND METHODS

The Southern Network on Adverse Reactions (SONAR) project conducts safety initiatives focusing on monoclonal antibody-associated PML. Case information was obtained directly from treating clinicians for four patients. We also obtained six reports from the FDA's Adverse Event Reporting System (AERS) of all BV-associated PML cases (search period August 1, 2011 to December 31, 2012); one of these cases was excluded as information confirming the diagnosis of PML was not included in the report and four were excluded as they represented duplicate reports of cases identified directly by SONAR. Duplicate reports in the FDA's AERS and the SONAR database were confirmed based on cross-referencing patient age, sex, and dates of BV treatment. Information obtained from clinicians was considered preferentially in instances where duplicate clinical information was available in AERS and from clinicians, based upon previous experience.[17] Inclusion criteria were receipt of BV therapy before PML diagnosis or symptom onset; PML confirmation based on histologic examination of tissue from the CNS or magnetic resonance imaging (MRI) showing lesions consistent with PML and documentation of JCV DNA in the cerebrospinal fluid (CSF) by polymerase chain reaction. Abstracted data included: sociodemographic information, neurological signs and symptoms at presentation, prior therapies, MRI findings, CSF findings, biopsy findings, and clinical outcomes. Two cases have been previously described as case reports (in three publications).[18–20]

FINDINGS

The five BV-associated PML cases range in age from 38 to 72 years (median, 50). (Table) Three patients were men. Indications for BV treatment included classical Hodgkin lymphoma (three patients) initially diagnosed seven, eight, and twelve years previously; primary cutaneous anaplastic large cell lymphoma diagnosed 4 years previously; and transformed mycosis fungoides.

The three patients with classical Hodgkin lymphoma were HIV-negative and had received standard front-line and salvage combination chemotherapy regimens. Initial therapy was ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) for all three Hodgkin lymphoma patients. The patients also received autologous stem cell transplantation (three and five years previously for two patients and immediately following BV for one patient) after standard salvage regimens using combination chemotherapy ICE (ifosfamide, carboplatinum, etoposide (two patients)), and ESHAP (etoposide, methylprednisolone, cytarabine, cisplatinum (one patient)). Two Hodgkin lymphoma patients also received radiation therapy to the abdomen and pelvis. The three patients had participated in clinical trials of BV and had responded to BV therapy. In evaluating neurologic dysfunction (described below), initial brain MRI scans revealed multifocal white matter lesions in these three patients. JCV DNA was not detected on at least one occasion in CSF samples obtained from two of these patients, one of whom had an immunostain of a spinal cord lesion biopsy (at the level of the first thoracic vertebra) positive for JCV, and the second for whom repeat CSF evaluation was positive.

The two patients with cutaneous lymphomas had not participated in clinical trials of BV. They received BV as an off-label treatment for their lymphoma. The patient with transformed mycosis fungoides was HIV-negative and initially diagnosed with stage IB mycosis fungoides four years prior to transformation. This patient had received topical corticosteroids, topical nitrogen mustard, phototherapy, interferon alpha, bexarotene, localized radiation therapy, and the histone deacetylase inhibitor romidepsin prior to BV therapy. The patient responded to BV therapy. In evaluating neurologic dysfunction, this patient underwent a brain MRI scan that revealed multifocal white matter lesions. A brain autopsy revealed JCV positive cells detected by in-situ hybridization. JCV had not been detected in CSF obtained prior to death in this patient. The patient with primary cutaneous anaplastic large cell lymphoma was also HIV-negative. The patient had received topical corticosteroids, methotrexate, bexarotene, denileukin diftitox, interferons alfa and gamma, pralatrexate, and the histone deactylase inhibitor vorinostat previously. The patient also responded to BV treatment. A brain biopsy revealed scattered demyelination and immunohistochemistry demonstrated oligodendrocytes positive for JCV.

The most common clinical presentations of PML in this series were speech dysfunction/aphasia (four patients); hemiparesis (two patients); hemianopsia (one patient); memory loss (two patients); gait dysfunction (three patients); and confusion (two patients). (Table) Onset of neurological symptoms occurred days to weeks following administration of two to six doses of BV (1.2 mg/kg to 1.8 mg/kg intravenously) in four patients. One patient (with classical Hodgkin lymphoma) underwent an autologous stem cell transplantation seven weeks after the last of six BV treatments and neurologic symptoms developed over the next four months. In four patients, neurological dysfunction rapidly and progressively worsened over a period of three to eight weeks until death occurred in hospice settings. The 38 year old patient with primary cutaneous anaplastic large cell lymphoma showed clinical and MRI findings suggestive of PML-associated immune reconstitution inflammatory syndrome (PML-IRIS).[18] The diagnosis of PML-IRIS was further supported by infiltrating T-cells identified on brain biopsy. The patient improved clinically and radiographically on daily oral prednisone. When corticosteroids were tapered off several months later, a new contrast enhancing lesion developed on brain MRI reflecting reactivation of PML-IRIS. Upon restarting prednisone, this brain lesion regressed and the patient has not had further lesion formation and partial neurologic recovery after several months follow-up while continuing on prednisone therapy.

DISCUSSION

This is the first comprehensive case series reporting five cases of PML among patients treated with BV, four of whom died within weeks of the PML diagnosis. In interpreting our findings, several factors should be considered.

First, there are important differences in the clinical features noted in patients who developed PML after BV treatment when compared to PML after exposure to the monoclonal antibodies rituximab, efalizumab, and natalizumab.[6] Time to onset of symptoms and duration of therapy before PML was much shorter in the BV cases. Three of the PML patients were symptomatic after only two or three doses of BV (administered every three

weeks) and the fourth was symptomatic after the fifth dose. In contrast, PML was diagnosed at a median of 63 weeks following initial exposure to rituximab. For natalizumab, PML symptom onset occurred after a median 26 months of treatment.[21] For efalizumab, all three confirmed cases developed three or more years after treatment initiation.[22] It is also important to note that the case-fatality rate is low for natalizumab (22%) versus 80% for BV, 90% for rituximab, and 100% for efalizumab.[13, 22–23]

Second, in the HIV-negative population, lymphoid malignancies, hematopoietic transplantation, and multi-agent chemotherapy are all risk factors associated with the development of PML. Thus, they are potential confounders in the assessment of the association between PML and BV. Three patients in this series had a history of relapsed classical Hodgkin lymphoma and had received multiple lines of combination chemotherapy and autologous transplantation. PML onset was three years and five years following transplantation in two of these patients. While in the third patient PML occurred six months after autologous transplantation. Previous case series suggest that most hematopoietic transplant associated PML cases among persons with lymphoid malignancies occur within 24 months of the transplant procedure.[5] The remote nature of the transplant procedures in two of the three patients with classical Hodgkin lymphoma argue against this as a major contributing risk factor. Similarly, two of the five patients in this series had cutaneous lymphomas and had not previously received multi-agent chemotherapeutic regimens.

Third, consideration of possible mechanisms of PML causation by BV is warranted. Depletion of CD30 expressing activated T-cells could reduce JCV immune surveillance in the CNS, resulting in PML. Related to this, CD30 has been proposed as a therapeutic target on alloreactive activated T-cells causing acute graft versus host disease.[24] Just as depletion of CD30 positive T-cells might be beneficial in graft versus host disease, it may also reduce immune surveillance in patients predisposed to JCV reactivation and PML.

Fourth, there is an incomplete understanding of what factors may influence development of and outcomes associated with PML-IRIS among the small number of persons who developed this syndrome after receiving immune modulating monoclonal antibody therapies. Among 52 previously reported non-Hodgkin lymphoma patients with PML who received rituximab, PML-IRIS was not noted.[13] This suggests that lymphoma patients, perhaps due to immune suppression related to previous treatments or the malignancy itself, may be less able to develop the immune response necessary for PML-IRIS. In contrast, all forty recently reported multiple sclerosis patients with natalizumab-associated PML developed PML-IRIS (a syndrome that is commonly noted among HIV-infected individuals with PML) after withdrawal of natalizumab and undergoing plasmapheresis.[23] The development of PML-IRIS shortly after the last dose of BV in the sole survivor of BV-associated PML represents the first case of PML-IRIS in a person with lymphoma who developed PML following therapy with rituximab or BV.[6,13] As highlighted in a recent report of PML in association with compounded dimethyl fumarate, development of PML-IRIS after drug discontinuation supports a causal relationship.[25] A prolonged course of corticosteroids may also be required to facilitate neurologic recovery in patients with PML-IRIS, as observed in the survivor in this case series and suggested in previous literature.[9]

Fifth, our results have clinical implications. The findings reinforce the importance of maintaining a high index of suspicion for PML when evaluating BV treated patients who present with speech disturbances, neurocognitive changes, and/or other persistent neurological symptoms. The presence of multifocal white matter lesions on brain MRI performed on classical Hodgkin lymphoma patients should further raise suspicion for PML, given the extreme rarity of multifocal CNS spread of classical Hodgkin lymphoma.[24] Health care providers should also be aware that even when JCV DNA is not detected during CSF sampling, PML remains a possibility due to the low sensitivity of tests used to detect JCV DNA in the CSF.[27] JCV DNA was not detected in CSF obtained from two patients, although it was later identified on CNS biopsy specimens from these patients. JCV DNA was detected in only one of two CSF samples obtained from a third patient. Thus, in the setting of a high index of suspicion, brain biopsy may be required to confirm or exclude a diagnosis of PML. More sensitive PCR assays are being developed to help overcome these challenges.[28]

There are some limitations to this study. Detailed clinical histories and medical records were available for the PML episode for four patients and an FDA safety report for the fifth patient. These data sources did not include information on prior infectious complications or leukopenia episodes that may have occurred with prior treatments. Also, data on the total number of persons who have received BV are not available, limiting our ability to estimate the incidence of BV-associated PML.

Our findings have policy implications. One consideration would be to develop a BV-related FDA-approved Risk Evaluation and Mitigation Strategy (REMS) program modeled after the one established for natalizumab (TOUCH ® (Tysabri Outreach: Unified Commitment to Health)). A REMS program is grounded in the concept of risk/benefit tradeoffs, primarily for beneficial drugs associated with important risks where the REMS ensures that patients and providers understand risks and benefits before starting treatment with the pharmaceutical agent.

We conclude that PML is a possible adverse drug reaction that may occur shortly after initiating BV treatment and after a few doses of BV have been administered. For patients with relapsed classical Hodgkin lymphoma, systemic anaplastic large cell lymphoma, or transformed cutaneous lymphoma, the high response rates from BV among persons with these diagnoses who otherwise have few treatment options supports favorable risk-benefit profiles in these settings.[29–30] In contrast, the decision to administer BV to patients with indolent cutaneous CD30+ lymphomas, such as cALCL and lymphomatoid papulosis, should be made in careful consideration of alternative options that, like BV, have high response rates and produce cosmetic benefits, but may have more favorable risk profiles.

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REFERENCES

1. Cinque P, Casari S, Bertelli D. Progressive multifocal leukoencephalopathy HIV, highly active antiretroviral therapy. N Engl J Med. 1998 Sep 17; 339(12):848–849. [PubMed: 9750081]
2. Sacktor N. The epidemiology of human immunodeficiency virus-associated neurological disease in the era of highly active antiretroviral therapy. Journal of neurovirology. 2002 Dec; 8(Suppl 2):115–121. [PubMed: 12491162]
3. Brooks BR, Walker DL. Progressive multifocal leukoencephalopathy. Neurologic clinics. 1984 May; 2(2):299–313. [PubMed: 6503939]
4. Garcia-Suarez J, de Miguel D, Krsnik I, Banas H, Arribas I, Burgaleta C. Changes in the natural history of progressive multifocal leukoencephalopathy in HIV-negative lymphoproliferative disorders: impact of novel therapies. American journal of hematology. 2005 Dec; 80(4):271–281. [PubMed: 16315252]
5. Shitrit D, Lev N, Bar-Gil-Shitrit A, Kramer MR. Progressive multifocal leukoencephalopathy in transplant recipients. Transplant international : official journal of the European Society for Organ Transplantation. 2005 Jan; 17(11):658–665. [PubMed: 15616809]
6. Carson KR, Focosi D, Major EO, Petrini M, Richey EA, West DP, et al. Monoclonal antibody-associated progressive multifocal leucoencephalopathy in patients treated with rituximab, natalizumab, and efalizumab: a Review from the Research on Adverse Drug Events and Reports (RADAR) Project. The lancet oncology. 2009 Aug; 10(8):816–824. [PubMed: 19647202]
7. Tan IL, McArthur JC, Clifford DB, Major EO, Nath A. Immune reconstitution inflammatory syndrome in natalizumab- associated PML. Neurology. 2011; 77:1061–1067. [PubMed: 21832229]
8. Harrison DM, Newsome SD, Skolasky RL, McArthur JC, Nath A. Immune reconstitution is not a prognostic factor in progressive multifocal leukoencephalopathy. J Neuroimmunol. 2011; 238:81–86. [PubMed: 21840066]
9. Major EO. Progressive multifocal leukoencephalopathy in patients on immunomodulatory therapies. Annual review of medicine. 2010; 61:35–47.
10. Ransohoff RM. Natalizumab for Multiple Sclerosis. New England Journal of Medicine. 2007; 356(25):2622–2629. [PubMed: 17582072]
11. Fox RJ, Rudick RA. Risk stratification and patient counseling for natalizumab in multiple sclerosis. Neurology. 2012 Feb 7; 78(6):436–437. [PubMed: 22282644]
12. [cited 7/24/2013] FDA Public Health Advisory Updated Safety Information about Raptiva (efalizumab. 2009. Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm110605.htm
13. Carson KR, Evens AM, Richey EA, Habermann TM, Focosi D, Seymour JF, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood. 2009 May 14; 113(20):4834–4840. [PubMed: 19264918]
14. [cited 2013 March 27, 2013] National Cancer Institute website: FDA Approval for Brentuximab Vedotin. 2011. Available from: http://www.cancer.gov/cancertopics/druginfo/fda-brentuximabvedotin
15. [cited May 24, 2013] Adcetris (brentuximab vedotin) package insert (8/19/2011). 2011. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125388s000,125399s000lbl.pdf
16. [cited March 27, 2013] Adcetris (brentuximab vedotin) package insert (1/13/2012). 2012 Jan 13. 2012; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125388s0005lbl.pdf
17. Bennett CL, Nebeker JR, Yarnold PR, et al. Evaluation of serious adverse drug reactions: A proactive pharmacovigilance program (radar) vs safety activities conducted by the food and drug

administration and pharmaceutical manufacturers. Archives of Internal Medicine. 2007; 167(10): 1041–1049. [PubMed: 17533207]

18. Jalan P, Mahajan A, Pandav V, Bekker S, Koirala J. Brentuximab associated progressive multifocal leukoencephalopathy. Clinical neurology and neurosurgery. 2012 Dec; 114(10):1335–1337. [PubMed: 22472351]
19. Wagner-Johnston ND, Bartlett NL, Cashen A, Berger JR. Progressive multifocal leukoencephalopathy in a patient with Hodgkin lymphoma treated with brentuximab vedotin. Leukemia & lymphoma. 2012 Nov; 53(11):2283–2286. [PubMed: 22424602]
20. von Geldern G, Pardo CA, Calabresi PA, Newsome SD. PML-IRIS in a patient treated with brentuximab. Neurology. 2012 Nov 13; 79(20):2075–2077. [PubMed: 23115213]
21. Bloomgren G, Richman S, Hotermans C, Subramanyam M, Goelz S, Natarajan A, et al. Risk of Natalizumab-Associated Progressive Multifocal Leukoencephalopathy. New England Journal of Medicine. 2012; 366(20):1870–1880. [PubMed: 22591293]
22. Molloy ES, Calabrese LH. Therapy: Targeted but not trouble-free: efalizumab and PML. Nature reviews Rheumatology. 2009 Aug; 5(8):418–419.
23. Tan IL, McArthur JC, Clifford DB, Major EO, Nath A. Immune reconstitution inflammatory syndrome in natalizumab-associated PML. Neurology. 2011 Sep 13; 77(11):1061–1067. [PubMed: 21832229]
24. Zeiser R, Nguyen VH, Hou JZ, Beilhack A, Zambricki E, Buess M, et al. Early CD30 signaling is critical for adoptively transferred CD4+CD25+ regulatory T cells in prevention of acute graft-versus-host disease. Blood. 2007 Mar 1; 109(5):2225–2233. [PubMed: 17068147]
25. van Oosten BW, Killestein J, Barkhof F, Polman CH, Wattjes MP. PML in a Patient Treated with Dimethyl Fumarate from a Compounding Pharmacy. New England Journal of Medicine. 2013; 368(17):1658–1659. [PubMed: 23614604]
26. Gerstner ER, Abrey LE, Schiff D, Ferreri AJ, Lister A, Montoto S, et al. CNS Hodgkin lymphoma. Blood. 2008 Sep 1; 112(5):1658–1661. [PubMed: 18591379]
27. Marzocchetti A, Di Giambenedetto S, Cingolani A, Ammassari A, Cauda R, De Luca A. Reduced rate of diagnostic positive detection of JC virus DNA in cerebrospinal fluid in cases of suspected progressive multifocal leukoencephalopathy in the era of potent antiretroviral therapy. Journal of clinical microbiology. 2005 Aug; 43(8):4175–4177. [PubMed: 16081969]
28. Ryschkewitsch CF, Jensen PN, Major EO. Multiplex qPCR assay for ultra sensitive detection of JCV DNA with simultaneous identification of genotypes that discriminates non-virulent from virulent variants. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2013 Apr 22.
29. Younes A, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012 Jun 20; 30(18):2183–2189. [PubMed: 22454421]
30. Pro B, Advani R, Brice P, Bartlett NL, Rosenblatt JD, Illidge T, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012 Jun 20; 30(18):2190–2196. [PubMed: 22614995]

Table

Clinical findings for five patients with brentuximab vedotin-associated PML

	Hodgkin's lymphoma	**Hodgkin's lymphoma[4, 6]**	**Hodgkin's lymphoma**	**Cutaneous anaplastic T-cell lymphoma[5]**	**Stage IB Mycosis Fungoides**
Clinical trial participant	Yes (5th PML case submitted to the FDA and the manufacturer- 11/2012)	Yes (1st PML case submitted to the manufacturer and to the FDA- 7/04/2011)	Yes (3rd PML case submitted to manufacturer and FDA- 11-15-2011)	No (2nd PML case submitted to the FDA- 10/2011)	No (4th PML case submitted to the manufacturer and to the FDA- 3/29/2012)
Age at time of PML diagnosis, gender	51, male	47, male	50, male	38, female	72, female
Speech/ mental status	Difficulty with word finding; confusion; forgetfulness over several weeks	Dysarthria; encephalopathy	Dysarthria	Mixed non-fluent aphasia, apraxia	Poor short term memory; confusion
Motor	Normal	Left hemiparesis; Impaired coordination	Right leg weakness and difficulty writing with right arm weakness	Mildly decreased strength in all extremities	Generalized weakness
Gait	Normal	Impaired due to hemiparesis	Impaired due to right leg weakness	Ataxia- requiring one person assist	Not tested
Vision	Normal	Left-sided hemianopsia	Normal	Normal	Normal
Differential diagnosis at time of PML presentation	PML or viral encephalitis- based on clinical and MRI findings	Ischemic stroke	Subacute CNS ischemia or progression of lymphoma	Metastatic brain lesions	PML- based on clinical findings and MRI findings
Detection of JCV	CSF- JCV DNA detected by PCR	CSF- JCV DNA detected by PCR in second LP, No JCV detected in initial LP.	Spinal cord lesion biopsy- initially negative for JC virus. Later evaluation of the sample by Genzyme detected JC virus. JC virus not detected in CSF from two lumbar punctures.	Brain biopsy- JCV detected by immunohistochemistry.	Brain autopsy with JCV detected by in situ hybridization. JCV not detected in CSF.
MRI	Multifocal areas of non-enhancing T2 white matter; greatest in the anterior/inferior right frontal lobe. Additional areas of subcortical T2 hyperintensity in bilateral temporal lobes.	T2 hyperintense lesion in right cerebral hemisphere with well circumscribed enhancing lesions in right parietal lobe.	Ill-defined abnormal T2 hyperintensity involving left superior cerebellar peduncle.	Multifocal white matter lesions left more than right hemisphere	Asymmetric T1 hypointense and T2 hyperintense lesions of the frontal white matter
Other illnesses	Thyroid cancer; thyroidectomy;	Diet controlled diabetes mellitus; depression	Epilepsy; migraine headaches	Severe eczema	None

	Hodgkin's lymphoma	Hodgkin's lymphoma[4, 6]	Hodgkin's lymphoma	Cutaneous anaplastic T-cell lymphoma[5]	Stage IB Mycosis Fungoides
	chronic lymphopenia chronic lymphopenia				
Prior medications (between 9–12 years prior to PML)			ABVD[1]; radiation to abdomen and pelvis	Topical steroid creams	
Prior Medications (between 5–8 years prior to PML)		Broad-field radiotherapy and ABVD[1]	ICE[4] (for relapse)- with partial response; BEAM; autologous stem cell transplant;	Topical steroid creams	
Between 3 and 4 years prior to PML		ESHAP[2], (for relapse); BEAM[3], autologous stem cell transplant	Localized radiation therapy to right neck (for second recurrence- nodular sclerosing Hodgkins disease)	Topical steroid creams	Topical corticosteroids, nitrogen mustard, phototherapy, interferon alfa-2b
Between 1 and 2 years prior to PML		gemcitabine, vinorelbine, and liposomal doxorubicin	None	Methotrexate, Targretin, denileukin diftitox, interferon gamma-1b; interferon alfa-2b	Topical corticosteroids, nitrogen mustard, phototherapy, interferon alfa-2b
< 1 year prior to brentuximab vedotin	ABVD[1]			Targretin, denileukin diftitox, interferon gamma-1b; interferon alfa-2b; vorinostat; praletrexate	Bexarotene, radiation therapy, romidepsin
Following brentuximab vedotin	Autologous stem cell transplantation; ICE[4]		Augmented ICE[4] (two cycles)	Prednisone	
# of doses of brentuximab vedotin and clinical response	6 doses (1.2 mg/kg q week). Total of two cycles of three doses. PET scan became negative following last brentuximab vedotin dose.	3 doses (1.8 mg/kg) – 21 days apart (PET showed favorable response to therapy).	5 doses (1.8 mg/kg)- clinical trial participant- withdrawn due to peripheral neuropathy; 2 additional doses (1.2 mg/kg)	2 doses (1.8 mg/kg q 3 weeks)- (one cycle). Disappearance of skin tumors.	Three doses (significant response of skin lesions)
Subsequent course	Progressive neurological deterioration. Died eight weeks after PML diagnosis.	Progressive neurological deterioration and worsening MRI. Died in hospice 8 weeks after PML diagnosis.	Progressive neurological deterioration and worsening MRI findings; T1–T2 and T8–T9 intramedullary lesions; Radiation therapy (3000 Gy) to T1–T2 lesion and corticosteroids. Paraplegia developed. Died in hospice six weeks after PML diagnosis and 20 weeks after first brentuximab vedotin treatment.	Neurological and radiological improvement- maintained on prednisone 50 mg orally/day for a year. Upon discontinuing corticosteroids, a new enhancing brain lesion developed. The patient restarted prednisone 20 mg orally/day with resolution of this lesion and no evidence for new lesions.	Progressive neurological deterioration. Died in hospice 15 weeks after first brentuximab vedotin treatment.

	Hodgkin's lymphoma	Hodgkin's lymphoma[4, 6]	Hodgkin's lymphoma	Cutaneous anaplastic T-cell lymphoma[5]	Stage IB Mycosis Fungoides
Time from first brentuximab vedotin to main PML symptoms	36 weeks. Six months following the autoSCT- confusion; forgetfulness; difficulty finding words	3 weeks- impaired coordination, left > right dysiadokinesis, slurred speech, left sided hemianopsia and visual neglect, left hemiparesis, and left central facial paresis.	24 weeks; speech changes; incoordination of right hand (poor penmanship) and right lower extremity weakness.	3 weeks- mixed aphasia, inability to read, and unsteady gait.	7 weeks- disorientation, poor short-term memory, and weakness

1 doxorubicin, bleomycin, vinblastine, and dacarbazine;

2 etoposide, methylprednisolone, cytarabine, cisplatin;

3 carmustine, etoposide, cytarabine and melphalan;

4 ifosfamide, carboplatin,