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Case Report

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Severe infusion reactions to brentuximab vedotin in two patients with Hodgkin lymphoma previously treated with allogeneic stem cell transplantation

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Abstract
Brentuximab vendotin is a monoclonal antibody approved in August 2011 for use in patients with Hodgkin disease and a rare systemic lymphoma known as anaplastic large cell lymphoma. Brentuximab is approved in patients with Hodgkin disease who have failed autologous transplantation or after failure of at least two prior multi-agent chemotherapy regimens but has not been studied following allogeneic transplantation. Four patients with relapsed Hodgkin disease have been treated at our institution with at least two doses of brentuximab vendotin. Two patients have experienced significant infusion reactions on multiple occasions, and two patients have tolerated the infusions well. During phase 2 trials, there were no reports of Grade 3 or 4 infusion-related reactions. Both patients with reactions had relapsed following allogeneic stem cell transplants, while neither of the patients who tolerated the infusions had undergone transplantation. We report our experience with brentuximab vendotin-treated patients at our institution, focusing on the two post-allogeneic patients who experienced multiple significant infusion reactions. This report evaluates possible mechanisms behind their reactions, including previous allogeneic stem cell transplantation as a likely precipitating factor.

Keywords
Brentuximab vedotin, Hodgkin lymphoma, infusion reaction, allogeneic hematopoietic stem cell transplantation

Introduction

Hodgkin disease (HD) affects approximately 8800 individuals in the United States each year.[1] In over 90% of patients with early-stage disease, cure can be achieved with standard chemotherapy involving doxorubicin, bleomycin, vinblastine, and dacarbazine.[2]

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Across all stages greater than 80% of patients are cured with combination chemotherapy and radiation.[3] Of those patients who will require treatment for refractory/relapsed disease, high-dose chemotherapy followed by autologous stem cell transplantation is the standard of care in eligible patients and has demonstrated cure rates of 40–70%.[3] Allogeneic transplant, though curative, is reserved for those patients refractory to autologous transplant secondary to a treatment-related mortality of approximately 25% and long-term survival of 30–40%.[4] Treatment options for patients relapsing post-transplant are limited to clinical trial and brentuximab vendotin approved in August 2011.

Brentuximab vendotin is a monoclonal antibody approved for use in patients with HD and a rare lymphoma known as systemic anaplastic large cell lymphoma (sALCL). It is the first agent approved for sALCL, and the first new agent to be approved for HD in over 30 years. Patients with sALCL may be eligible to receive brentuximab after failure of at least one prior chemotherapy regimen. In patients with HD, it is approved for those who have failed autologous transplantation or after failure of at least two prior multi-agent chemotherapy regimens, but clinical trials excluded patients who had undergone allogeneic transplantation.[5] Brentuximab ventodin is a chimeric IgG1 antibody directed toward CD30, a marker frequently found on the Reed Sternberg cells characteristic of HD. The antibody is conjugated to monomethyl auristatin E (MMAE), a microtubule disrupting agent. Once bound to the target cell, the entire antibody conjugate is internalized and induces cell kill by releasing MMAE to disrupt the intracellular microtubule complex.

Four patients with relapsed HD have been treated at our institution with at least two doses of brentuximab vendotin. Two patients have experienced significant infusion reactions on multiple occasions, and two patients have tolerated the infusions well. Both patients with reactions were allogeneic stem cell transplant recipients, while neither of the patients who tolerated the infusions has undergone transplantation.

We report our experience with brentuximab vendotin–treated patients at our institution, focusing on the two post-allogeneic patients who experienced multiple significant infusion reactions. This report discusses possible mechanisms behind their reactions, including previous allogeneic stem cell transplantation as a likely precipitating factor.

Case reports

Patient #1: LG

LG is a 21-year-old female who was originally diagnosed with HD in 2007. Over the course of 3 years, she was treated with multiple cycles of chemotherapy, radiation, and a full myeloablative allogeneic peripheral blood stem cell transplant with cyclophosophamide and busulfan. One year following her transplant, a PET scan indicated disease recurrence, and she began treatment with brentuximab vendotin. At the time of treatment initiation, the patient had no evidence of chronic graft-versus-host disease (cGVHD) and was not receiving any immunosuppression.

Prior to her first cycle, LG was given dexamethasone, palonosetron, and diphenhydramine as premedications 30 minutes prior to chemotherapy administration. A total dose of 87 mg (1.8 mg/kg) of brentuximab was administered in 118 milliliters (mL) of normal saline (NS) over 30 minutes. The chemotherapy nurse documented that the patient ''tolerated [the] infusion well'' with ''no acute distress.''

The patient returned 3 weeks later for her second cycle. She received the same premedication as were given with the first cycle and the same dose of brentuximab was initiated. The infusion was stopped after 15 minutes due to patient complaints of ''feeling funny'', coughing, dry heaving, and itching. She also described feeling that her eyes were swollen; her face felt ''big'', and her throat felt like it was ''closing off.'' Vital signs revealed a blood pressure of 110/68 mmHg, pulse of 114 beats/min, and oxygen saturation of 98%. She was given a fluid bolus, hydrocortisone, diphenhydramine, and lorazepam. The decision was made to send the patient home and resume the infusion the following morning. When she returned the next morning, she was given diphenhydramine and dexamethasone as premedications 30 min prior to chemotherapy administration. Due to the cost of the drug, she was given a test dose to evaluate her response prior to preparing the entire dose. A dose of 25 mg was administered in 55 mL of NS over 10 min, which she tolerated well. The remainder of the drug was infused over 30 min without complication. Five minutes following completion, the patient complained of pruritis and erythema on her hands and feet. She was given diphenhydramine and lorazepam to take at home.

With her third cycle, the patient was instructed to take scheduled oral famotidine, diphenhydramine, acetaminophen, and dexamethasone 2 days prior to her chemotherapy infusion, and lorazepam was added to the premedication regimen. The brentuximab infusion was interrupted after 10 min due to tachycardia and erythema in her face and neck. She was given a fluid bolus and hydrocortisone. The infusion was restarted at a slower rate, and LG continued to report erythema and pruritis on her hands and feet. Hydrocortisone and diphenhydramine were repeated to facilitate completion of the infusion.

LG received her fourth cycle of brentuximab as an inpatient. She received diphenhydramine,

acetaminophen, and hydrocortisone prior to the infusion, and her brentuximab dose was increased slightly to 92 mg due to a weight increase. Hospital records indicate that she did experience a reaction to the chemotherapy including facial swelling, dyspnea, and a rash on her upper extremities. The infusion was interrupted and restarted at a decreased rate with no further complications.

Patient #2: MC

MC is a 23-year-old female diagnosed with nodular sclerosing HD in 2003. Over the course of 8 years, she was treated with multiple chemotherapy regimens, radiation, an autologous stem cell transplant, and a full allogeneic stem cell transplant from a matched related donor. Approximately 2 years following her allogeneic transplant, a PET scan was suggestive of relapse. She began treatment with additional chemotherapy but required treatment delays and ultimately discontinuation due to cytopenias. The decision was made to initiate treatment with brentuximab vendotin. At the time of treatment initiation, the patient was approximately 3 years post-transplant, had a history of mild skin cGVHD, and was not on any immunosuppressive medications.

With her first cycle, MC was given palonosetron, dexamethasone, and diphenhydramine as premedications 30 min prior to chemotherapy administration. A total dose of 176 mg (1.8 mg/kg) was infused and was tolerated well.

Three weeks later, she presented for her second cycle. Identical premedications were administered and the same dose of brentuximab was initiated. Fifteen minutes into the infusion, the patient described feeling feverish and having difficulty breathing. The infusion was stopped and she was given a second dose of diphenhydramine and one dose of hydrocortisone. This event occurred on the same day as the second cycle infusion for LG (patient #1), and because both experienced these unexpected reactions, MC was also asked to return the following day to complete her infusion. When she returned, she was given the same three premedications and a test dose of brentuximab, which was tolerated well. She completed the remaining chemotherapy infusion without immediate complication. However, on the following day, the patient called the infusion clinic complaining of chest pain and shortness of breath. She was asked to come to the clinic, where she was given diphenhydramine, acetaminophen, corticosteroids, and albuterol to take at home.

Prior to her third treatment cycle, the patient was instructed to take scheduled oral famotidine, diphenhydramine, acetaminophen, and dexamethasone 2 days prior to her chemotherapy infusion. At the infusion clinic MC was premedicated with palonosetron, dexamethasone, ranitidine, diphenhydramine, methylprednisolone, and lorazepam. There was no dose change to her brentuximab. A single dose of methylprednisolone was given halfway through the infusion, which was completed without interruption. Once the infusion was finished, the patient began experiencing severe rigors and a temperature of 101.3°F. She was given acetaminophen, diphenhydramine, methylprednisolone, and placed on 2 liters of oxygen. The patient's pulse and blood pressure were also elevated, and emergency services were called for transport to the emergency department. She was released later that afternoon.

Discussion

In the two cases reported here, brentuximab administration was associated with delayed and progressive Grade 2/3 infusion reactions. This is unusual as infusion reactions to monoclonal antibodies occur most commonly with the first infusion and decrease with repeated doses.[6-8]

Infusion reactions with a clinical course as described above were unexpected. A search of MEDLINE (1948 – November 2011) using the terms *brentuximab*, *brentuximab vendotin*, *Adcetris*, *hypersensitivity*, *infusion reaction*, and *antibody* revealed no other case reports of delayed or progressive infusion reactions.

Due to the limited amount of published data for brentuximab vendotin outside the clinical trial setting, data from similar chimeric monoclonal antibodies used to treat hematologic malignancies were evaluated. Two types of reactions are commonly associated with the use of monoclonal antibodies: hypersensitivity reactions and acute infusion reactions induced by cytokine release. Hypersensitivity reactions to monoclonal antibodies primarily occur immediately within minutes of the initial drug infusion, making this an unlikely cause of the reactions our patients experienced. Approximately 90% and 77% of hypersensitivity reactions to cetuximab and rituximab, respectively, were observed with the first drug infusion.[6] Although possible mechanisms have been suggested, the exact mechanism behind monoclonal antibody hypersensitivity reactions is unknown.[6]

Infusion reactions to brentuximab vendotin are thus far only reported in the clinical trial literature and in one recently published case series. During phase I trials, two cases of anaphylaxis were reported. During phase 2 trials, there were no reports of Grade 3 or 4 infusion-related reactions, however, in 19 patients (12%) there were reports of Grade 1 or 2 infusion-related reactions. Chills (4%), nausea (3%), dyspnea (3%), pruritus (3%),

pyrexia (2%), and cough (2%) were the most common adverse reactions associated with infusion related reactions. It is unclear at what point during treatment these reactions occurred, and post-allogeneic transplant patients were excluded from these trials.

Acute infusion-related reactions induced by cytokine release occur when the antibody induces host immune activation for tumor cell kill. Many monoclonal antibodies such as rituximab exert their cytotoxic effects through activation of the complement system (CDCC) and recruitment of various endogenous immune effector cells (ADCC).[9] Similar to hypersensitivity reactions, these occur with the first infusion due to the presumably large number of circulating malignant cells. A series of case reports indicated that patients with high tumor burden are at an increased risk of experiencing infusion-related reactions with the first infusion of rituximab but are likely to tolerate subsequent infusions.[7] In a pooled analysis of over 350 non-Hodgkin's lymphoma patients treated with rituximab, it was found that the majority of infusion-related adverse events occurred within 24 hours following the first treatment.[8] CDCC and ADCC are dependent on external display of bound antibody. This type of reaction is unlikely in patients receiving brentuximab vendotin, as the entire antibody conjugate is internalized and induces cell kill by releasing MMAE to disrupt the intracellular microtubule complex, not through complement activation or cytokine recruitment.[10,11] In fact, early development of naked CD30 monoclonal antibodies failed to yield promising therapies, partially due to unsuccessful activation of effector cells.[10]

Despite considerable efforts to diminish the development of human anti-mouse antibodies (HAMA) through recombinant DNA technology, such an immune response is still possible with the use of chimeric and even humanized monoclonal antibodies.[12–14] There are reports of HAMA development toward brentuximab in both HD and sALCL patients, which was evaluated during phase 2 trials.[5] While 7% and 30% of patients developed persistently positive and permanently positive antibodies, respectively, only 1% experienced antibody-related adverse reactions to warrant therapy discontinuation. The overall number of adverse events (any grade) related to anti-brentximab antibodies is not reported.[5]

For the majority of patients, the clinical consequence of HAMA development is increased drug clearance and lack of antitumor effect with subsequent infusions due to changes in biodistribution and pharmacokinetic properties.[12] Reports of severe reactions to HAMA are few, and allergic or infusion-related events due to their presence have not been found to be significant.[12,13] Khazaeli et al. reported the effect of repeat chimeric or murine monoclonal antibody infusion in patients who were HAMA-positive. Of 42 infusions, only two cases of early and reversible anaphylaxis and two cases of mild allergic reactions (described as rash and flushing) were described.[13] Even so, this may be the most likely phenomena in our patient cases, as the initial infusions were tolerated well and reactions experienced with each subsequent administration. Anti-brentuximab antibody development was also noted in clinical trials, as described above. It is thus far unclear what consequence these antibodies may have on the efficacy of brentuximab treatment.

As previously noted, the two patients who did not tolerate brentuximab infusions had undergone allogeneic stem cell transplantation prior to receiving brentuximab; while the patients with no complications had not undergone transplantation. Both LG and MC had adequate renal function throughout their treatment courses and neither was receiving additional medications, which may have interacted with brentuximab to alter medication activity. It is possible that there is an additional immune-mediated interaction with brentuximab in the post allogeneic transplant setting. Increased levels of various cytokines are found in post allogeneic transplant patients, which could lead to exacerbation of the mechanisms described above.[15,16] Additionally, the expression of CD30, the target of brentuximab, is exclusive to cells of the immune system.[17] Active immune cells which express CD30 release soluble CD30 (sCD30), and this is measurable in serum.[17,18] Elevated sCD30 levels are found in some patients following allogeneic transplantation, particularly those with graft-versus-host disease.[17] We postulate that the increased activity of the immune system following transplantation, as well as its hyper-reactivity, may have contributed to the increased reactions with brentuximab.

Conclusion

It is important to note that neither patient described above has required drug discontinuation due to infusion-related adverse events. However, based on the published literature currently available for brentuximab vendotin and the reactions typically described with chimeric monoclonal antibodies, these episodes were unexpected in both their timing and severity. While two patients is certainly a small treatment population, having such similar experiences with the first two patients to receive this drug at our institution warranted further investigation.

Hypersensitivity to a component of the medication or an infusion reaction due to cytokine release is unlikely in these cases, as both patients tolerated the initial infusion well. While very few patients experience allergic-type reactions to HAMA development, this is the

most likely explanation, and perhaps the clinical manifestation of anti-brentuximab antibody development is more severe than described in clinical trial data. It is also possible that patients who have previously received an allogeneic stem cell transplant are at higher risk of developing an immune reaction after receiving brentuximab. Additional research is needed to further evaluate this interaction.

Centers administering this agent should be aware of the possibility of delayed infusion reactions that do not improve with repeated use, particularly in allogeneic transplant patients. Infusion rates may need to be adjusted and supportive care measures should be readily available.

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Conflict of Interest

None declared.

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