

# Brentuximab Vedotin Infusion Reaction Management: A Case Study

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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## CASE STUDY

We report a case of a grade 3 (Common Terminology Criteria for Adverse Events [CTCAE]) infusion reaction to brentuximab vedotin (Adcetris), in a patient with refractory Hodgkin lymphoma, at a large National Cancer Institute–designated cancer center in the Midwest (National Cancer Institute, 2010). Acute infusion reaction management and subsequent premedication strategies are outlined.

Ms. R is a 30-year-old woman who presented with stage IV Hodgkin lymphoma at the age of 29. Initial staging revealed lymphadenopathy above and below the diaphragm, as well as fluorodeoxyglucose (FDG)-avid lung lesions, splenic lesions, and multiple sites of bony involvement. Bone marrow biopsy was negative.

She was treated with six cycles of chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), to which she obtained a complete response by positron emission tomography-computed tomography (PET-CT) criteria. Ten months after chemotherapy completion, she presented with new PET-avid adenopathy in the cervical and paratracheal regions, and a biopsy revealed recurrent Hodgkin lymphoma. Salvage chemotherapy was administered with ifosfamide carboplatin, and etoposide (ICE). After two cycles of salvage chemotherapy, a PET-CT confirmed a complete response, and she proceeded to an autologous stem cell transplant with a preparative regimen of carmustine, etoposide, cytosine arabinoside, and melphalan (BEAM).

Brentuximab vedotin consolidation therapy was prescribed in the post-transplant consolidation setting, beginning 45 days after stem cell reinfusion, given the patient's high risk for recurrence. This strategy was based upon the results of the AETHERA phase III clinical trial (Moskowitz et al., 2015), showing improvement in progression-free survival with brentuximab vedotin consolidation therapy, post autologous transplant.

The first dose of brentuximab vedotin was administered without difficulty, at full dose (1.8 mg/kg) at a standard infusion time of 30 minutes. The second dose of brentuximab vedotin was complicated by nausea, chest pain, and dysphagia within 10 minutes of medication initiation. Upon the emergence of these symptoms, the brentuximab vedotin infusion was held. Vital signs were stable, with a temperature of 36.9°C, pulse 84, respirations of 20, and blood pressure of 107/67 mm

Hg. Oxygen saturations were 99% on room air. Diphenhydramine (50 mg) was administered intravenously (IV), along with 20 mg of IV famotidine. An electrocardiogram (ECG) was obtained, which was unremarkable, showing normal sinus rhythm. Fifteen minutes later, the symptoms of chest pain and shortness of breath persisted, so hydrocortisone at 100 mg IV was administered, with an additional 25 mg of IV diphenhydramine and 20 mg of IV famotidine. Intravenous granisetron was given for nausea. Thirty minutes after onset, the chest pain was persistent, and oxygen saturations were normal. Hydrocortisone (50 mg) was administered intravenously, and Ms. R's condition improved, with resolution of her symptoms within 30 minutes of the second hydrocortisone dose.

The brentuximab vedotin was restarted 30 minutes after symptom resolution at a decreased infusion rate to be administered over 60 minutes. Thirty minutes later, however, Ms. R developed tingling and numbness in her feet and tongue. The brentuximab vedotin infusion was again held, and 100 mg of IV methylprednisolone was administered. Ms. R's symptoms resolved within 40 minutes, and the brentuximab vedotin infusion was able to be continued over a prolonged period of more than 4 hours. Vital signs were checked every 15 minutes during the infusion reaction and remained stable throughout. The infusion was discontinued with 40 mg of drug remaining, due to the prolonged infusion time.

Given the clear benefits of brentuximab consolidation in improving progression-free survival post transplant (Moskowitz et al., 2015) in high-risk Hodgkin lymphoma, it was thought the benefit of brentuximab vedotin consolidation outweighed the possible risks of subsequent infusions.

Upon reviewing the available literature regarding brentuximab vedotin hypersensitivity reactions, which will be outlined in the discussion summary, we instituted the premedication strategy for subsequent infusions outlined in the Table on p 628.

Standard epinephrine and methylprednisolone were available at the bedside in the event of any anaphylactic reaction. This regimen was chosen based on the clinical rationale for H1 and H2 blockade, as well as corticosteroid and antipyretic coverage, in the prevention of hypersensitivity reactions, not classified as anaphylaxis. With the institution of the outlined premedications, Ms. R tolerated subsequent infusions well, at full dose and at standard infusion rates, with no documented infusion reactions, and was able to complete a total of 16 cycles of consolidation therapy.

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Infusion reactions have been reported with brentuximab vedotin therapy in both clinical trial settings (Younes et al., 2010) and in the post clinical trial experience (Baxley, Kumm, Bishop, Medina, & Holter-Chakrabarty, 2013). Infusion reactions can range from minor grade 1 infusion reactions, to anaphylactic reactions, requiring drug discontinuation.

Arora, Bhatt, Liewer, Armitage, and Bociel (2015), reported a case of successful brentuximab vedotin desensitization utilizing a 12-step desensitization protocol for anaphylactic reactions, with increasing dosage and rate over 3 subsequent infusions. Similarly, DeVita, Evens, Rosen, Greenberger, and Petrich (2014) reported a successful 13-step desensitization protocol for the treatment of anaphylaxis related to brentuximab vedotin, which was unresponsive to steroid, antipyretic, antihistamine, and H2 blockade premedications.

As our patient Ms. R had a grade 2 infusion reaction, but no anaphylaxis, we utilized a strategy of steroid, antipyretic, antihistamine, and H2 blockade premedications, without deployment of the full desensitization strategy as described by Arora et al. (2015) and DeVita et al. (2014). This strategy has permitted us to continue full-dose consolidation treatment with brentuximab vedotin without any subsequent infusion reactions. We believe this strategy will provide a useful tool for clinicians in the management of grade 2/3 infusion reactions.

## BACKGROUND

Antibody-drug conjugates (ADCs) are one of the newer types of chemotherapy agents. Brentuximab vedotin is an ADC consisting of a monoclonal antibody targeting CD30, which is overexpressed in Hodgkin lymphoma, and anaplastic large cell lymphoma, conjugated with monomethyl au-

**Table. Brentuximab Vedotin Hypersensitivity Premedication Protocol**

Medication	Route	Dose	Timing
Diphenhydramine	Oral	50 mg	30–60 minutes prior to infusion
Acetaminophen	Oral	650 mg	30–60 minutes prior to infusion
Dexamethasone	IV	20 mg	30 minutes prior to infusion
Famotidine	IV	20 mg	30 minutes prior to infusion

Note. IV = intravenous.

ristatin E (MMAE). This microtubule-disrupting agent (MMAE) causes cell death.

The drug was developed with the help of a technology lesson from the Indian Ocean sea hare, *Dolabella auricularia* (Bouchard et al., 2014). This sea animal harbors toxic substances that protect it from being eaten. From studying these toxic substances, there arose a drug class known as the auristatins. These auristatins are conjugated with monoclonal antibodies to make the ADC brentuximab. The ADC brentuximab attaches to the tumor-associated antigen, where it is internalized into the cell. Brentuximab then releases its cytotoxic agent, which causes cell death by mitotic disruption similar to the vinca alkaloids.

Brentuximab vedotin was first approved by the US Food and Drug Administration (FDA) for the treatment of Hodgkin lymphoma and anaplastic large cell lymphoma on August 19, 2011 (Senter & Sievers, 2012). It is approved for second-line therapy in Hodgkin lymphoma and anaplastic large cell lymphoma and as consolidation post autologous transplant in Hodgkin lymphoma (Moskowitz et al., 2015).

## INFUSION REACTIONS

Brentuximab vedotin, like many monoclonal antibodies, can produce infusion reactions. In phase I clinical trials, there were two cases of anaphylaxis reported. In phase II clinical trials, 12% of patients reported infusion-related reactions (Singh, Singh, & Bhorja, 2014).

There are two mechanisms thought to produce infusion-related reactions: anaphylaxis and anaphylactoid reactions. Anaphylaxis is a systemic reaction from the interaction between immunoglobulin E (IgE) and mast cells. Anaphylactoid reactions are cytokine-mediated, rather than IgE-mediated. Clinical manifestations tend to be simi-

lar in both types of reactions (Singh et al., 2014). The reactions most common with brentuximab vedotin are anaphylactoid, including chills, nausea, dyspnea, pruritus, pyrexia, and cough.

Patients in clinical trials for brentuximab vedotin were tested every 3 weeks for antibodies using a sensitive immunoassay. A total of 7% of patients developed positive antibodies, and 30% developed transiently positive antibodies. A higher incidence of infusion reactions were noted in these persistently positive patients. Patients were also noted to develop these reactions during the second dose, possibly allowing these antibodies to develop after the initial exposure to the medication. There are case reports of patients developing problems as far out as cycle 4.

Another interesting observation is that several of these reactions occurred in patients after transplant (DeVita et al., 2014). In the case study presented here, Ms. R was not tested for brentuximab antibodies, as she responded to conservative premedication strategies.

## DESENSITIZATION PROTOCOLS

There are several desensitization protocols available for patients who develop anaphylaxis to brentuximab vedotin. A standard 12-step protocol has been successfully used in several patients. The standard 12-step protocol may be used in severe reactions, but only a small subset of patients would require this intense method (Arora et al., 2015).

Another example of a rapid desensitization protocol involves premedication with prednisone at 50 mg at 24, 12, and 0 hours prior to infusion, followed by premedication with IV diphenhydramine, IV ranitidine, IV methylprednisolone (125 mg) and oral montelukast 30 minutes prior to the infusion (Arora et al., 2015). Another possible strategy was outlined earlier using oral diphenhydramine, oral

acetaminophen, IV dexamethasone, and IV famotidine 30 minutes prior to the infusion. Using these various strategies, we can safely infuse brentuximab vedotin to patients with few reactions. The choice of regimen can be made based on the severity of reaction, specifically to the patient. ●

### Disclosure

The authors have no potential conflicts of interest to disclose.

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