

Successful Desensitization to Brentuximab Vedotin After Anaphylaxis

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Clinical Practice Points

- Brentuximab vedotin is an antibody-drug conjugate indicated for anaplastic large cell lymphoma (ALCL) and Hodgkin lymphoma (HL) that has demonstrated clinical efficacy. Anaphylaxis has been reported as a reaction to brentuximab vedotin and in the past has necessitated discontinuation of therapy.
- We report a case of drug desensitization to brentuximab vedotin in a patient with relapsed ALCL who experienced anaphylaxis from the drug. The patient tolerated the desensitization to brentuximab vedotin well and was able to continue with therapy.
- The strategy we devised for desensitization to brentuximab vedotin may be an option for other patients who experience hypersensitivity reactions to this drug.

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Introduction

Targeting CD30, which is overexpressed in both Hodgkin lymphoma (HL) and anaplastic large cell lymphoma (ALCL), has been shown to be a promising alternative to traditional cytotoxic chemotherapy to treat these tumors.¹ Brentuximab vedotin is an antibody-drug conjugate that was developed by linking the anti-CD30 antibody cAC10 (SGN-30) with the antitubulin chemotherapeutic compound monomethyl auristatin E (MMAE).² It has shown in vitro selectivity and cytotoxicity in both ALCL and HL. In phase I clinical trials, brentuximab vedotin dosed every 3 weeks at the maximum tolerated dose of 1.8 mg/kg resulted in complete remission in 26% of patients and tumor regression in 86%.³ A phase II study showed a remission rate of 86%, with complete remission in 57% of patients using the same 3-week dosing schedule at 1.8 mg/kg.⁴ Adverse effects included peripheral neuropathy, fever, nausea, diarrhea, and neutropenia. One patient experienced anaphylaxis during the second drug infusion and was removed from the study. To our knowledge, desensitization to brentuximab vedotin has not been previously reported.

We report successful desensitization to brentuximab vedotin in a patient with a history of anaphylaxis to this drug, allowing for continuation of therapy.

Case Report

A 22-year-old man presented to our hospital after a hypersensitivity reaction to single-agent chemotherapy treatment with brentuximab vedotin. The patient was initially diagnosed with ALCL at 15 years of age. He had disease in the left mediastinal, axillary, and supraclavicular lymph nodes with no evidence of bone marrow infiltration. He underwent induction chemotherapy with vincristine, doxorubicin, and intrathecal methotrexate followed by maintenance therapy with vincristine and doxorubicin and continued intrathecal methotrexate infusion. He achieved complete remission (CR), but later he experienced a relapse with left axillary disease when he was 19 years old. He was treated with 2 cycles of ifosfamide, carboplatin, and etoposide (ICE) followed by autologous stem cell transplantation, and again achieved CR. One year later, he experienced another relapse, this time with pulmonary nodular involvement, and was treated with weekly vinblastine followed by an allogeneic stem cell transplantation from a matched sibling donor. This was complicated by graft-vs.-host disease of the lung and liver that was amenable to steroid therapy. At age 22 years, he experienced another relapse of disease in the inguinal lymph nodes, leading to initiation of brentuximab vedotin 1.8 mg/kg infused every 21 days.

He received his first dose of brentuximab vedotin after premedication with 1 g acetaminophen and 50 mg diphenhydramine.

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Desensitization to Brentuximab After Anaphylaxis

Beginning 1 week after the first cycle of therapy, he began to experience significant myalgia and neuropathic pain. He was therefore premedicated with dexamethasone starting 4 days before his next infusion in addition to receiving acetaminophen and diphenhydramine 1 hour before the infusion. With the second dose of brentuximab vedotin, he experienced itching in the arms and legs 3 minutes into the infusion. He then became flushed and felt tightness in his throat. He alerted the nursing team of his symptoms 13 minutes into the infusion. At that time, he had stridor and wheezing on examination accompanied by tachycardia and hypotension. He was treated with epinephrine plus intravenous fluids, diphenhydramine, ranitidine, and hydrocortisone. He also received 2 doses of nebulized albuterol. His symptoms rapidly improved after receiving epinephrine. He was monitored in the hospital overnight and discharged home the next day.

Despite the patient's severe reaction, it was decided that brentuximab vedotin represented the best and preferred therapeutic option. The course of his reaction and rapid response to epinephrine was highly suggestive of an IgE-mediated mechanism, making drug desensitization plausible. The predictive value of skin testing for brentuximab vedotin allergy is unknown, and there was concern that skin testing could lead to skin necrosis from the highly toxic chemotherapeutic nature of monomethyl auristatin E. The potential risk and unknown benefit of skin testing combined with the urgent need for treatment and the patient's history of anaphylaxis led us to forego skin testing and move directly to drug desensitization. The desensitization strategy, modified from Brennan et al, used a 3-bag method with the following dilutions of the drug in saline: 0.005 mg/mL for bag 1, 0.05 mg/mL for bag 2, and 0.545 mg/mL for bag 3.⁵ The patient required a treatment dose of 125 mg (1.8 mg/kg) of brentuximab vedotin. A 12-step protocol was designed, leading to

doubling of the dose in each step, with a maximum infusion rate of 80 mL/h (43.5 mg/h) during the final step, to a cumulative dose of 125 mg (Table 1).

The patient was admitted to our intermediate care unit (step-down intensive care unit). He had experienced myalgia after the first infusion, so his chemotherapy protocol had been adjusted to include 4 days of premedication with oral dexamethasone 4 mg per day, which he had completed before the admission. For the purposes of desensitization, he was also treated with oral famotidine 20 mg, diphenhydramine 50 mg, cetirizine 10 mg, and acetaminophen 1 g 1 hour before starting the desensitization protocol. The decision to premedicate was based on the severity of the patient's reaction and the urgent necessity of successful drug administration. Oncology nursing staff was present on the patient's floor for drug handling and infusion setup, whereas the nursing staff from our step-down unit supervised the desensitization process. The patient underwent the 12-step desensitization protocol lasting 323 minutes without any reactions. He was monitored overnight and discharged home the following day. He continued to receive brentuximab vedotin every 3 weeks with 3 successful desensitization procedures completed, for a total of 4 doses.

The patient underwent repeated imaging of his primary tumor site 2 weeks after his third dose of brentuximab vedotin. His inguinal mass had decreased in size, measuring 5.4×5.4 cm before starting brentuximab and 2.7×2.1 cm after the 3 cycles of brentuximab vedotin. It was also noticeably decreased on examination.

After the fourth dose of brentuximab vedotin, the patient experienced worsening of his neuropathic pain. He was unable to achieve relief with gabapentin or narcotics and ultimately elected to stop receiving brentuximab given the severity of the neuropathic

Table 1 Protocol for Desensitization to Brentuximab Vedotin^a

Solution Preparation						
		Amount of Drug (mg)	Total Volume (Normal Saline) (mL)	Concentration (mg/mL)		
Solution 1		1.25	250	0.005		
Solution 2		12.5	250	0.05		
Solution 3		136.25	250	0.545		
Desensitization Steps						
Step	Solution	Rate (mL/h)	Time (min)	Volume per Step (mL)	Administered Dose (mg)	Cumulative Dose (mg)
1	1	2	15	0.5	0.0025	0.0025
2	1	5	15	1.25	0.0063	0.0088
3	1	10	15	2.5	0.0125	0.0213
4	1	20	15	5	0.025	0.0463
5	2	5	15	1.25	0.0625	0.1088
6	2	10	15	2.5	0.125	0.2338
7	2	20	15	5	0.25	0.4838
8	2	40	15	10	0.5	0.9838
9	3	10	15	2.5	1.3625	2.3463
10	3	20	15	5	2.725	5.0713
11	3	40	15	10	5.45	10.5213
12	3	80	158	210.7	114.4788	125
TOTAL	323 min	256.2 mL				

^aPreparation of solutions is outlined in the upper portion of the table. Desensitization steps are listed in the lower portion.

pain. He continues therapy with an individualized treatment plan using weekly vinblastine infusions.

Discussion

This report describes a successful desensitization strategy for brentuximab vedotin. To our knowledge, this is the first report of desensitization to this drug. This particular patient had multiply relapsed disease; therefore, being able to continue to have brentuximab vedotin as a potential therapeutic option was important. He experienced no other symptoms of IgE-mediated reactions using this desensitization strategy; unfortunately, he was ultimately unable to continue with the medication owing to another drug toxicity, neuropathic pain.

Rituximab is another monoclonal antibody that is directed against CD20. It is used therapeutically to target B cells in both oncologic and inflammatory diseases. Rituximab and other monoclonal antibodies have been identified as causing severe life-threatening reactions resulting from cytokine-release syndrome (CRS), which leads to an increase in circulating inflammatory cytokine levels within 90 minutes of the infusion.⁶⁻⁸ Patients experiencing CRS may have rigors, chills, fever, headache, nausea, and fatigue. In severe cases, sepsis and even death may occur.^{6,9} CRS-related reactions frequently occur with the very first drug exposure, and symptoms usually begin within 1 hour of drug administration. The incidence of CRS seems to correlate with the rate of infusion and tumor burden; therefore, the infusion rate is often decreased for patients who experience infusion reactions with rituximab. Anaphylaxis to rituximab has also been described and appears to be a distinct phenomenon.¹⁰ We believed that our patient's symptoms (itching, shortness of breath, hives) and the timing of his symptoms (he tolerated the first dose without reaction and then experienced symptoms within minutes of the second infusion) were more consistent with an IgE-mediated reaction rather than CRS. For that reason, we chose to proceed with a traditional desensitization regimen rather than simply decreasing the maximum infusion rate. One possible mechanism for further

verifying an IgE-mediated reaction would have been to look for brentuximab-specific IgE in the patient, as has been reported in anaphylaxis to rituximab¹¹; however, we were unable to do this for our patient. Nonetheless, his ability to tolerate the infusion without further symptoms of anaphylaxis, and the subsequent decrease in his tumor size indicate the efficacy of the desensitization.

Conclusion

Drug desensitization should be considered for patients who experience an anaphylaxis reaction to brentuximab vedotin.

Disclosure

The authors have stated that they have no conflicts of interest.

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