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## **Brentuximab Vedotin Desensitization in a Patient with Refractory Hodgkin Lymphoma**

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**Running Title:** Brentuximab vedotin desensitization

## **Abstract**

Brentuximab vedotin has emerged as a useful treatment option for relapsed or refractory Hodgkin lymphoma; however, uncommon cases of anaphylactic reactions may require its permanent discontinuation. We report a 29-year-old woman with refractory Hodgkin lymphoma, who developed an anaphylactic reaction during the second dose of brentuximab vedotin. A 12-step desensitization protocol was followed; after premedicating with antihistaminic agents, methylprednisone and montelukast, a total dose of 156 mg of brentuximab vedotin (1.8 mg/kg) was given as three infusions with increasing rate and concentration. Such desensitization protocol can allow safe administration of brentuximab vedotin and may have a broader applicability in managing hypersensitivity reactions with other monoclonal antibodies.

**Key Words:** brentuximab vedotin, anaphylaxis, desensitization, Hodgkin's lymphoma

Brentuximab vedotin is an antibody-drug conjugate that links the anti-CD 30 monoclonal antibody cAC10 to the antitubulin cytotoxic agent monomethyl auristatin E. Single agent brentuximab vedotin results in an overall response rate of 75% in refractory/relapsed Hodgkin lymphoma (1). Hence, it is currently approved in the US for Hodgkin lymphoma after the failure of autologous stem cell transplant (ASCT) or at least two prior multi-agent chemotherapy regimens in patients ineligible for ASCT. Brentuximab vedotin is also been studied to induce a response before ASCT (2), in combination with bendamustine in first relapse (3) and after ASCT in high-risk patients to improve progression-free survival (4). Additionally, brentuximab vedotin is being integrated in upfront therapy with excellent complete response rate (5). An international randomized trial comparing doxorubicin, vinblastine, dacarbazine and brentuximab vedotin to doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) is ongoing now. Although brentuximab vedotin is a valuable drug, cases of anaphylactic reactions can require drug discontinuation (6). We report a case of successful desensitization to brentuximab vedotin in a patient, who developed an anaphylactic reaction to the drug. This approach enabled us to continue the therapy.

A 29-year-old woman presented with stage IV nodular sclerosis Hodgkin lymphoma and was treated with nine 2-weekly treatments (four-and-a half cycles) of the ABVD regimen followed by another two treatments without bleomycin due to a reduction in her measured pulmonary diffusion capacity. At that point, she developed progressive painful left axillary lymphadenopathy and significant fatigue. A positron emission tomography (PET) scan demonstrated an improvement in initial sites of disease but new hypermetabolic left axillary lymphadenopathy with a maximum standard uptake value (SUV) of 8. A biopsy of a left axillary

lymph node confirmed residual Hodgkin lymphoma. Given the primary refractory disease, there were concerns about tolerance of further conventional chemotherapy in this patient. After a lengthy discussion, therefore, the patient was started on intravenous brentuximab vedotin (1.8 mg/kg) and tolerated the first dose without any side effects. However, within 5 minutes of infusion of the second dose, she developed anaphylaxis (hives, angioedema, dyspnea, wheezing and tachycardia), which was successfully controlled with steroids and antihistamines. Brentuximab was believed to represent an easier salvage option, hence rapid desensitization protocol was utilized.

The patient received oral prednisone (50mg) at 24 hours, 12 hours and 0 hours prior to hospitalization. She was pre-medicated with IV diphenhydramine (50mg), IV ranitidine (50mg), IV methylprednisolone (125 mg) and oral montelukast (10 mg) before the next infusion of brentuximab vedotin. A total dose of 156mg of brentuximab vedotin (1.8 mg/kg) was given as three infusions with increasing rate and concentration (Table 1 and 2). Epinephrine and hydrocortisone were kept at the bedside. The patient developed nausea and vomiting 2 hours into her final dose, hence a dose of IV diphenhydramine, ranitidine, and methylprednisolone were repeated. Following this, the patient completed her infusion without further difficulty. The patient was readmitted 3 weeks later to receive the 3<sup>rd</sup> dose of brentuximab vedotin following the same desensitization protocol and she completed the infusion without any difficulty. However, the patient required one cycle of salvage therapy with ifosfamide, carboplatin and etoposide for refractory disease. She then underwent high dose carmustine, etoposide, cytarabine, and melphalan chemotherapy followed by ASCT and achieved complete remission.

## Discussion

Hypersensitivity reactions to brentuximab vedotin seems to be the result of initial sensitization during the first infusion, and reactions of progressive severity occur during subsequent infusions (7), as was seen in our patient. It is speculated that brentuximab vedotin hypersensitivity reactions may be mediated by human anti-mouse antibodies, the latter were reported in clinical trials (7). Anaphylactic reactions, although uncommon, may require drug discontinuation. Prior reports have demonstrated successful use of desensitization in a few patients with hypersensitivity reactions to brentuximab vedotin (Table 3) (7-10). Although the use of brentuximab vedotin was off-label in this patient, this was felt to be an easier option for the patient. A phase II trial has demonstrated a role of brentuximab vedotin in inducing remission before ASCT for refractory patients (2). Hence, the patient underwent a 12-step desensitization protocol.

During desensitization, sub-threshold doses of antigen may result in monomeric binding to the IgE receptor, leading to internalization of the antigen-receptor complex (instead of the crosslinking that occurs when a higher amount of antigen is present). This may prevent subsequent activation of mast cells and basophils (11). However, other researchers have suggested that low doses of antigen may induce rearrangement of the cell membrane in antigen-sensitized mast cells that prevents the internalization of the antigen/Ig E/Fc epsilon RI (receptor for IgE) complex and protects against anaphylaxis (12).

A standardized 12-step protocol has been successfully used in patients with immediate hypersensitivity to many drugs such as carboplatin, cisplatin, doxorubicin, rituximab and penicillins (13). Patients may experience mild breakthrough reactions during as many as 30% of desensitization, hence the clinician's experience in managing such situation is critical. Breakthrough symptoms are managed by stopping the infusion temporarily, administering further treatments and restarting the protocol again at the step that elicited symptoms. The protocol should be adjusted to advance through the problematic step more gradually if it is to be performed again in the same patient (12). Our patient experienced mild nausea and vomiting, which were easily managed with steroids and antihistamines.

In conclusion, as illustrated by this report, drug desensitization can allow safe administration of brentuximab vedotin after a hypersensitivity reaction. Such desensitization protocol may have a broader applicability in managing hypersensitivity reactions with other monoclonal antibodies.

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**Table1. Drug Concentration for Desensitization to Brentuximab Vedotin**

|            | Amount of Drug<br>(mg) | Total Volume (Normal Saline)<br>(ml) | Concentration<br>(mg/ml) |
|------------|------------------------|--------------------------------------|--------------------------|
| Solution 1 | 0.05                   | 10 mL syringe                        | 0.005                    |
| Solution 2 | 0.95                   | 19 mL syringe                        | 0.05                     |
| Solution 3 | 155                    | 284 mL                               | 0.545                    |

The brentuximab vial was reconstituted to yield a concentration of 5 mg/mL. A dilution of brentuximab was compounded by adding 1 mL (5 mg) of brentuximab to 99 mL of NS to yield a concentration of 0.05 mg/mL. The brentuximab dilution was used to prepare the first dose of 0.05 mg. A total volume of 1 mL of the brentuximab dilution was withdrawn and added to 9 mL of NS and dispensed in a syringe (solution 1). The second dose of brentuximab was prepared by withdrawing 19 mL of the 0.05mg/mL brentuximab dilution and dispensed in a second syringe (solution 2). The final 155 mg of brentuximab was prepared per the manufacturer's recommendations and dispensed in a total volume of 284 mL to yield a concentration of 0.545 mg/mL (solution 3).

**Table2. Protocol for Desensitization to Brentuximab Vedotin**

| Step | Solution | Rate<br>(ml/hr) | Time<br>(minute) | Volume<br>per Step<br>(ml) | Administered<br>Dose (mg) | Cumulative<br>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              | 200.20           | 266.933                    | 145.4787                  | 156                     |

Table 2 describes the 12 step protocol for brentuximab desensitization. For each step, the specific solution, rate of administration, length of infusion, dose infused and the cumulative dose infused are described. For example, in step 1, “solution 1” is infused at 2 mL/hr for 15 minutes. A total volume of 0.5 mL (0.0025 mg of drug) is infused before proceeding to step two.

**Table 3. Published cases of desensitization of brentuximab vedotin in relapsed lymphoma**  
 AlloSCT indicates allogeneic stem cell transplant; ALCL anaplastic large-cell lymphoma, ALK

| Study                  | Age (year), Sex | Lymphoma          | Number of prior therapies           | Anaphylaxis during cycle of brentuximab * | Desensitization protocol                                                                                                                           | Total cycles of brentuximab received | Outcome after brentuximab                                                                                            |
|------------------------|-----------------|-------------------|-------------------------------------|-------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| Current Patient        | 29y/F           | HD                | Primary refractory                  | 2 <sup>nd</sup> cycle                     | 12-step                                                                                                                                            | 3 cycles                             | Switched to third-line chemotherapy/A SCT                                                                            |
| Story SK et al(9)      | 57/F            | Mycosis fungoides | 4                                   | 2 <sup>nd</sup> cycle                     | 13-step                                                                                                                                            | Several cycles                       | Partial response                                                                                                     |
| DeVita MD et al(8)     | 32/F            | ALCL-ALK negative | >4 including ASCT                   | 4 <sup>th</sup> cycle                     | 13- step                                                                                                                                           | 16 cycles                            | Remained in CR.                                                                                                      |
| O'Connell AE et al(10) | 22/M            | ALCL              | >2 including alloSCT                | 2 <sup>nd</sup> cycle                     | 12 step                                                                                                                                            | 4 cycles                             | Initial clinical improvement f/b switch over to vinblastine due to neuropathic pain worsening caused by brentuximab. |
| Baxley AA et al(7)     | 21y/F           | HD                | Multiple including alloSCT          | 2 <sup>nd</sup> cycle                     | 2 <sup>nd</sup> , 3 <sup>rd</sup> & 4 <sup>th</sup> cycle: slow infusion of drug over 30minutes after patient tolerated test dose and premedicated | 4 cycles                             | --                                                                                                                   |
|                        | 23/F            | HD                | Multiple including ASCT and alloSCT | 2 <sup>nd</sup> cycle                     | 2 <sup>nd</sup> & 3 <sup>rd</sup> cycle: infusion given after premedications.                                                                      | 3 cycles                             | --                                                                                                                   |

anaplastic lymphoma kinase, ASCT autologous stem cell transplant, CR complete response, HD Hodgkin's lymphoma

\*Indicates the cycle when the patient developed allergic reaction for the first time