

# Rapid desensitization to brentuximab vedotin after severe anaphylaxis in the treatment of refractory Hodgkin's lymphoma

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## Abstract

**Introduction:** Brentuximab vedotin is a monoclonal antibody drug conjugate used for the treatment of patients with Hodgkin lymphoma. Hypersensitivity reactions to brentuximab vedotin may include cutaneous, cardiovascular, respiratory, gastrointestinal and neurological signs and symptoms.

**Case report:** We present the case of a 23-year-old Mexican female with stage IV progressive classical nodular sclerosing Hodgkin lymphoma who received multiple previous chemotherapy regimens. Brentuximab vedotin at 1.8 mg/kg (180 mg total dose), for 21-day cycles was indicated. Within 5 min of infusion of the 5th cycle of brentuximab, she developed severe anaphylaxis (hives, angioedema, diaphoresis, tachycardia, dyspnea, hypoxemia and loss of consciousness), which was successfully controlled with epinephrine, steroids and antihistamines.

**Management and outcome:** Intradermal skin test at a concentration of 0.1 mg/ml was positive. Due to the severity of the symptoms and the lack of access to alternative treatments, we performed a desensitization protocol. A total of 180 mg of brentuximab was given in three bag solutions in 12 steps, with an initial concentration dose of 1/100 of the total dose in a course of 5.56 h with no hypersensitivity reactions.

**Discussion:** Severe anaphylaxis has been reported in 1.2% of patients receiving brentuximab vedotin. Patients who are treated by rapid drug desensitization with their first option therapy present a favorable survival rate with better cost-effectiveness in comparison to second-line treatment.

## Keywords

Brentuximab, desensitization, anaphylaxis, Hodgkin's lymphoma

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## Introduction

Biologic agents are immune modulators used to treat different diseases, including inflammatory diseases and malignancies.<sup>1</sup> They can be grouped into three main categories, including cytokines, antibodies, and fusion proteins. Monoclonal antibodies (mAbs) have developed to soluble proteins like cytokines, to cell surface molecules, to immunoglobulin E (IgE) and to tumor antigens.<sup>2</sup>

The clinical presentation of hypersensitivity reactions (HSR) to mAbs may include cutaneous, cardiovascular, respiratory, gastrointestinal and neurological

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signs and symptom. In some cases, patients may display fever, chills or myalgia.<sup>3</sup>

Brentuximab vedotin (BV) is a mAb-drug conjugate that delivers monomethyl auristatin E into CD-30 expressing cells and was approved as monotherapy by the US Food and Drug Administration (FDA) for the treatment of patients with Hodgkin lymphoma after the failure of autologous stem cell transplantation or at least two prior multi-agent chemotherapy.<sup>4</sup>

## Case description

We present the case of a 23-year-old Mexican female with stage IV progressive classical nodular sclerosing Hodgkin lymphoma, with mediastinal, bilateral axillary, retroperitoneal, cervical lymph nodes, and splenic involvement.

She was treated with three cycles of chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), without response. Subsequently, she was treated with cyclophosphamide, gemcitabine, and vinorelbine for three cycles achieving a partial response, followed by autologous stem cell transplantation but progressed after three months. She was then treated with three cycles of cyclophosphamide, carboplatin and etoposide plus low-dose nivolumab achieving a partial response with a Deauville 3 score. At the time, the patient was asymptomatic and chose to remain in watchful waiting, developing new lesions and B symptoms after five months of follow-up.

The patient started intravenous treatment with brentuximab vedotin monotherapy at 1.8 mg/kg (180 mg total dose), on day 1 of each 21-day cycle. The first four cycles of brentuximab were given without reactions. However, within 5 min of infusion of the 5th cycle of brentuximab, she developed severe anaphylaxis (hives, angioedema, diaphoresis, tachycardia, dyspnea, oxygen desaturation and loss of consciousness), which was successfully controlled with epinephrine, steroids and antihistamines.

Skin prick test to brentuximab was performed at a concentration of 10 mg/ml and compared with a negative control of glycerinated solution with a negative result, 1 × 1 mm wheal in both tests. The intradermal test at a concentration of 0.1 mg/ml was positive with a

14 × 11 mm wheal compared to the negative control (glycerinated solution) 1 × 1 mm wheal.

Due to the severity of the symptoms and the failure of alternative treatments, we decided to perform a desensitization protocol. She was premedicated with intravenous chlorpheniramine (10 mg), methylprednisolone (60 mg) and ondansetron (8 mg) before the infusion of brentuximab vedotin.

A total of 180 mg of brentuximab was given in three bag solutions with a dilution of 1:100, 1:10 and 1:1 of the total dose (Table 1) in 12 steps, with increasing rate and concentration every 15 min (Table 2). Fluids with normal saline solution at 100 mL/h throughout the first 11 steps with an increase to 250 mL/h after step 12. Every three weeks she was readmitted to receive the same desensitization protocol until she completed 10 cycles, without presenting hypersensitivity reactions. The patient presented a decrease in the size and presence of lesions in the control PET-CT but without achieving complete remission, followed by adjuvant treatment with Nivolumab and allogeneic hematopoietic cell transplantation.

## Discussion

The use of mAbs has increased dramatically and is currently the cornerstone of targeted therapies for cancer. Parallel to the increased use of mAbs, an increase in hypersensitivity reactions (HSRs) has been observed. The prevalence of any kind of HSRs to mAbs is difficult to quantify because it is a large and actively increasing drug category.<sup>5</sup>

Reactions to mAbs include infusion reactions resulting from cytokine release and/or immune complex generation. They can occur on the first exposure or after multiple exposures, similar as what can be seen with platinum compounds.<sup>6</sup>

Anaphylaxis is the most serious of all allergic reactions and can be fatal. This reaction has been reported with a large number of biological agents.<sup>7</sup>

In clinical trials using brentuximab vedotin as monotherapy, 13% of patients experienced an infusion reaction, out of which 1.2% of patients had severe anaphylaxis.<sup>8</sup> HSRs to BV seem to be the result of initial sensitization during the first infusion, and reactions of

**Table 1.** Rapid desensitization to brentuximab vedotin three bags.

| 3 Bag solution/<br>12 steps              | Volume (mL)<br>per bag | Concentration<br>(mg/mL) per bag | Amount (mL)<br>of bag infused | Dose infused<br>(mg) per bag |
|------------------------------------------|------------------------|----------------------------------|-------------------------------|------------------------------|
| Solution 1                               | 250                    | 0.0072 mg/ml                     | 9.38                          | 0.068 mg                     |
| Solution 2                               | 250                    | 0.072 mg/ml                      | 18.75                         | 1.35 mg                      |
| Solution 3                               | 250                    | 0.714 mg/ml                      | 250                           | 178.58 mg                    |
| Total dose: 180 mg total time (h) = 5.67 |                        |                                  |                               |                              |

**Table 2.** Rapid desensitization to brentuximab vedotin 12 steps.

| Steps | Solution | Rate (ml/h) | Time (min) | Volume per step (ml) | Administered dose (mg) | Cumulative dose (mg) |
|-------|----------|-------------|------------|----------------------|------------------------|----------------------|
| 1     | 1        | 2.5 ml/h    | 15         | 0.625 ml             | 0.0045 mg              | 0.0045 mg            |
| 2     | 1        | 5 ml/h      | 15         | 1.25 ml              | 0.009 mg               | 0.0135 mg            |
| 3     | 1        | 10 ml/h     | 15         | 2.5 ml               | 0.018 mg               | 0.0315 mg            |
| 4     | 1        | 20 ml/h     | 15         | 5 ml                 | 0.036 mg               | 0.0675 mg            |
| 5     | 2        | 5 ml/h      | 15         | 1.25 ml              | 0.09 mg                | 0.158 mg             |
| 6     | 2        | 10 ml/h     | 15         | 2.5 ml               | 0.18 mg                | 0.338 mg             |
| 7     | 2        | 20 ml/h     | 15         | 5 ml                 | 0.36 mg                | 0.698 mg             |
| 8     | 2        | 40 ml/h     | 15         | 10 ml                | 0.72 mg                | 1.418 mg             |
| 9     | 3        | 10 ml/h     | 15         | 2.5 ml               | 1.79 mg                | 3.21 mg              |
| 10    | 3        | 20 ml/h     | 15         | 5 ml                 | 3.57 mg                | 6.78 mg              |
| 11    | 3        | 40 ml/h     | 15         | 10 ml                | 7.14 mg                | 13.9 mg              |
| 12    | 3        | 80 ml/h     | 174.4      | 232.5 ml             | 166.1 mg               | <b>180 mg</b>        |

progressive severity occur during subsequent infusions. It is speculated that BV HSRs may be mediated by human anti-mouse antibodies which has been reported in the clinical trials. Patients in clinical trials for BV were tested every three weeks for antibodies using a sensitive immunoassay. A total of 7% of patients developed positive antibodies, and 30% developed transiently positive antibodies. Similarly to the case presented, there are other reports of patients developing problems as far out as cycle 4 and a higher incidence of infusion reactions were noted in these persistently positive patients.<sup>9</sup>

This is the first report of rapid successful desensitization to this drug in severe anaphylaxis. This particular patient had multiply relapsed disease, and therefore being able to continue to have BV as a potential therapeutic option which was essential for her prognosis and quality of life.

Desensitization allows receiving first-line treatment in hypersensitivity reactions, where there is no alternative drug; the drug has a unique mechanism of action or has few adverse effects, providing a better prognosis and quality of life.

### Research ethics and patient consent

Research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Written and informed consent was obtained from the patient to participate. Written and informed consent for publication was obtained from the patient. The patient was informed that de-identified data would be used in the scientific research and publications.

### Authors' contributions

Rosalaura Virginia Villarreal-Gonzalez: design of the work, analysis, interpretation of data, drafting and final approval of the version. Integrity of any part of the work are appropriately investigated and resolved.

Sandra Nora González Díaz: design of the work, analysis, interpretation of data, drafting and final approval of the version.

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Andres Gomez-De Leon: design of the work, analysis, interpretation of data, drafting and final approval of the version.

Natalhie Acuña-Ortega: design of the work, analysis, interpretation of data, drafting and final approval of the version.

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