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Case Report

Classic Hodgkin Lymphoma Treated with Brentuximab Vedotin

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Abstract

Classical Hodgkin lymphoma (cHL) is a highly curable malignancy, even in advanced stage disease with long-term disease specific survival exceeding 85%. Brentuximab vedotin (BV) is an antibody-drug conjugate targeting CD30, is one of the novel therapies that is showing promising results when used in conjunction with frontline treatment for cHL such as doxorubicin. These promising results have been demonstrated since 2018, during which the hallmark ECHELON-1 trial was conducted and eventually led to the approval of BV as part of the initial treatment for advanced stage cHL. A case of a 35-year-old man initially diagnosed with Stage IIB cHL presented with respiratory complications secondary to a large anterior mediastinal mass. The patient was treated with BV in combination with doxorubicin, vinblastine, and dacarbazine (AVD) instead of the first line regiment doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) without complications. This case is unique due to the demonstration of an uncomplicated and exceptional clinical response to BV-AVD in a patient who could not be treated with first-line ABVD due to severe restrictive lung disease and concern for tracheal stenosis.

Keywords: Classical Hodgkin Lymphoma; Brentuximab Vendotin; BV-AVD; Involved Site Radiation Therapy

Introduction

Classical Hodgkin lymphoma (cHL) is a highly curable malignancy, even in advanced stage disease, with long-term disease specific survival exceeding 85% [1]. However, about 20–30% of the patients do not respond to traditional therapies while 45–55% of those who respond will later relapse or progress despite treatments [2]. Brentuximab vedotin (BV), an antibody-drug conjugate targeting CD30, is one of the novel therapies that is showing promising results when used in in conjunction with frontline treatment for cHL: the anthracycline doxorubicin, the vinca alkaloid vinblastine, and the alkylating agent dacarbazine. While the combination of these three medications plus the antineoplastic antibiotic bleomycin (ABVD) is considered the standard form of treatment for cHL, a modified-standard treatment comes in the form of omitting bleomycin from the combination (AVD) [2]. Brentuximab vedotin (BV) was initially approved by the United States Food and Drug Administration for the treatment of HL after failure of autologous hematopoietic stem cell transplant or after failure of at least two prior lines of multiagent chemotherapy in patients who are not transplant candidates [3]. However, the ECHELON-1 trial showed that BV-AVD had superior efficacy for progression-free survival after 2 years of use in patients with

untreated, advance staged HL compared with those receiving the standard ABVD treatment [4]. This hallmark study led the US FDA to approve BV as part of the initial treatment of advanced stage HL [5]. Here we present a case of stage IC cHL in a 31-year-old male being treated with combination therapy BV-AVD followed by involved-site radiotherapy without complications.

Case

A 31-year-old male presents to the emergency department with complaints of severe dyspnea and chest discomfort that increasingly worsened over 3-4 days. At the time of presentation, the patient confirmed fatigue, weakness, weight loss, night sweats, dyspnea, and chest tightness. He denied any chest pain, fevers, and chills. His past medical history was significant for nodular sclerosing type Classic Hodgkin Lymphoma diagnosed one year previously via biopsy of the lymph node of the neck. However, it was never treated due to multiple social constraints. The diagnosis was complicated by frequent pleural effusions that required placement of bilateral Pleur-X catheter and frequent thoracentesis. His last bone marrow biopsy performed around the time of diagnosis was negative for lymphoma involvement. No other significant co-morbidities were noted in his past medical history. Family history was not remarkable.

Physical exam was positive for superficial, deep, and posterior cervical adenopathy of the right side, bilateral supraclavicular adenopathy, and extensive pectoral lymphadenopathy with a large anterior chest mass. There was no evidence of any significant organomegaly or disease below the diaphragm (Figure 1). On initial presentation, the patient was afebrile temperature 98.9 F, tachycardic at 127 beats per minute, and had blood pressure of 143/85 mmHg. Due to respiratory distress, he was placed on 2L nasal cannula and saturated well at 98%. His labs are significant for leukocytosis of 27 x 103/uL with neutrophil predominance 74%, hemoglobin of 411.6 g/dL, platelets 571 x 103 uL, and lactate dehydrogenase 450 U/L. His complete metabolic panel is within normal limits. Transthoracic echocardiogram was negative for structural defects. It was positive for a moderate loculated pericardial effusion overlying the left ventricle. Computed tomography (CT) angiogram of the chest revealed bulky pathologic adenopathy in the supraclavicular region, anterior to the sternum, axillary regions, and mediastinum (Figure 2). Pulmonary function testing revealed severe decreases in FVC (38% of predicted), FEV1 (36%), total lung capacity (38%), residual volume (44%), and DLCO (41%), indicating severe restrictive lung disease. FVC/FEV1 ratio was 81. Based on the above findings, the patient was deemed to be at least Stage IIB, IPS 3 (International Prognostic Scoring). Initially there was a concern for tracheal stenosis on imaging, however given the patient's stable clinical presentation it was determined that the patient's airways were patent and did not require tracheal stenting. Bleomycin was eliminated as a potential treatment option due to the extensive pulmonary involvement of his disease and the concern for pulmonary fibrosis as a potential adverse effect. The patient was therefore offered the following chemotherapy regiment with curative intent: brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine (BV-AVD) for 28-day cycles. One day after receiving his first cycle of BV-AVD, the patient reported new-onset back pain and gait instability. MRI of the entire spine was ordered and revealed a 66 x 15 x 8 mm intrathecal extra-axial mass of T5 through T7 with resulting mass effect on the spinal cord. The patient received Decadron and underwent palliative radiation therapy of T3 through T8 for 10y over five fractions. On discharge, his anterior chest wall mass has shrunken significantly (Figure 3) with increased strength in his bilaterally lower extremities, indicating a good response to the BV-AVD regiment. Laboratory workup showed significant improvement in leukocytosis from 27 x 10^3/uL to 10 x 10^3/uL.

Figure 1: Initial clinical presentation. Extensive superficial, deep, and posterior cervical (red arrows) adenopathy of the right side, bilateral supraclavicular adenopathy, and extensive pectoral lympadenopathy with a large anterior chest mass seen on physical exam (yellow arrows).

Figure 2: Computed tomography (CT) angiogram of the chest revealed bulky pathologic adenopathy in the supraclavicular region, anterior to the sternum (red arrows), axillary regions, and mediastinum.

Figure 3: Significant size reduction of anterior chest wall mass size after 1 cycle of BV-AVD (black arrows).

At his 2-month follow-up, the patient noted continued shortness of breath, appetite, weight loss, and generalized fatigue but otherwise had no new symptoms. He still requires continued back pain and required a wheelchair for mobility but reports improvement in energy and strength in his lower extremities. Repeat CT of the chest, abdomen, and pelvis after 4 cycles of BV-AVD demonstrated marked interval reduction of his supraclavicular, axillary, and mediastinal adenopathy. It also showed resolution of the large mass in the anterior chest wall. (Figure 4). He reports tolerating treatment well and plans to continue his prescribed BV-AVD regiment.

Figure 4: Computed tomography (CT) of the chest demonstrating significant reduction of the patient's previously extensive bulky adenopathy and complete reduction of his anterior chest mass (yellow arrows).

Discussion

Our patient initially presented with intrinsic compression of his trachea secondary to bulky supraclavicular adenopathy. At the time of presentation, his disease was tentatively determined to be at least Stage IIB due to the presence of systemic symptoms and bulky mediastinal disease. Per the National Comprehensive Cancer Network guidelines, treatment for Stage IIB cHL initially begins with two cycles of ABVD, after which the patient is re-staged and the treatment is adjusted if needed [6]. However, a recent phase II trial assessing the efficacy of BV-AVD in previously untreated early-stage unfavorable HL demonstrated an improved PET-negative rate when compared with ABVD [7].

There was significant concern for the use of bleomycin in this patient. Bleomycin has been shown to induce significant pulmonary toxicity and mortality in patients undergoing treatment with the drug. Due to the patient's tentative respiratory status on presentation, the choice was made to forego ABVD and to instead use BV-AVD, a therapy option that at that time had been newly

approved for patients with Stage III or higher cHL based on the results of the ECHELON-1 trial. 4 Of note, the patient had not yet had his MRI thoracic spine showing extra-nodal involvement when the decision to use BV-AVD was made. His clinical stage would later be adjusted to Stage IV with cord compression, IPS 3.

Previous studies have shown that when comparing BV in combination with ABVD and AVD in patients with cHL, patients who received BV-ABVD experienced a significantly higher incidence of pulmonary toxic effects when compared to those in the BV-AVD treatment arm [8]. It was shown that late-stage, treatment-naïve patients such as ours responded well to both BV-ABVD and BV-AVD, but 44% of the patients who received BV-ABVD had to stop due to pulmonary toxicity [8]. In the treatment of patients with advanced cHL, BV-AVD was found to have a 4.9% lower combined risk of progression, death, or incomplete response than ABVD [4]. However, it should be noted that BV is not without its own adverse effects. The ECHELON-1 trial found that patients receiving BV-AVD reported greater rates of peripheral neuropathy and neutropenia (67% and 58% respectively) compared with patients receiving ABVD (43% and 45%) [4]. Our patient did experience neurologic symptoms but the rapid onset of these symptoms combined with the finding of a spinal mass makes it less likely that these features were a result of starting BV-AVD.

Considering the recent approval of BV-AVD, it is important to also extend the discussion to include the possibility of combining BV-AVD with radiation therapy. In addition to BV-AVD, our patient also received palliative radiation to his thoracic spine. While not applicable to our patient, BV-AVD used in conjunction with 30 Gy involved site radiation therapy have shown promising results. A previous multicenter study assessing the efficacy of BV-AVD in patients with early-stage cHL followed by 30 Gy IS found that 93% of patients achieved a negative PET scan after completing the treatment. As with the aforementioned studies on the efficacy of BV-AVD, there was no evidence of significant pulmonary toxicity in the patients participating in this study [9]. A previous case in which a patient with cHL was treated with both BV and 36y ISRT also showed promise, achieving near complete response after 4 cycles of BV. However, that patient only received BV as a third-line option after failing treatment with first-line AVD and 36 Gy radiation therapy [10].

Upon completion of his first cycle of BV-AVD, our patient showed impressive improvement in terms of his bulky adenopathy and respiratory status. His neck mass had shrunken considerably by his day of discharge, and he was able to safely transition to breathing on room air. At his 2-month follow-up, he also noted that he had no new-onset or worsening pulmonary symptoms. By his 4th cycle of chemotherapy, he further reinforced that he was not experiencing any pulmonary symptoms, noting only back pain and lower extremity weakness due to his spinal tumor. In addition, his latest staging CT demonstrated a complete eradication of his anterior neck mass and a vast improvement in his bulky lymphadenopathy. The excellent treatment response without concern for pulmonary toxicity in our patient shows that BV-AVD is a viable option in cHL patients suffering from restrictive lung disease due to compression from bulky lymphadenopathy.

Conclusion

While ABVD has been the internationally accepted standard regimen for advanced-stage HL, BV-AVD has shown to be more effective in terms of symptom resolution and pulmonary toxic effect control, at least in late stage cHL in the treatment-naïve patient who cannot receive bleomycin due to restrictive lung disease. Further studies are needed to evaluate long term outcomes of the treatment compared to the traditional ABVD.

Data Availability Statement

All data generated or analyzed in this study are included in this article. Access to data is possible with permission from the responsible author.

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Consent for Publication

Written informed consent was obtained from the patient for publication of this case report.

Ethics Approval

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Conflict of Interest

The authors have no conflict of interest to declare.

All authors read and approved the final manuscript.

All listed authors made a significant scientific contribution to the research in the manuscript approved its claims and agreed to be an author.

Author Contribution

Study Design (A)

Data Collection (B)

Statistical Analysis (C)

Data Interpretation (D)

Manuscript Preparation (E)

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