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Adverse reactions related to brentuximab vedotin use: A real-life retrospective study

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Summary

Post-marketing data regarding brentuximab vedotin (BV) are sparse. The aim of this study was to assess the frequency and nature of significant adverse drug reactions (ADR) in patients treated with BV in a real-world setting. We conducted a systematic retrospective study of patients treated with BV in a French university hospital. Significant ADR were collected using the electronic patient records. Between January 2009 and December 2016, 39 patients received BV. Median age was 43.2 and 53.8% were males. Overall, 20 patients (51.3%) experienced at least one significant ADR and 24 reactions were reported in total. Twelve (50%) out of 24 ADR were severe. The most frequently observed significant ADR were peripheral sensory neuropathy and CMV reactivation. ADR led to drug discontinuation for 4 patients and dose reduction for 6 patients. Only 29.2% of the events were spontaneous reported. Prospective monitoring is needed to better assess BV safety.

KEYWORDS
Brentuximab vedotin; Hodgkin lymphoma; Systemic anaplastic large cell lymphoma; Adverse drug reactions; Post-marketing surveillance

Abbreviations
ADR: adverse drug reactions
ALCL: anaplastic large cell lymphoma
ASCT: autologous stem cell transplantation
BV: brentuximab vedotin
CMV: cytomegalovirus
CTCAE: common toxicity criteria of adverse events
EMA: European medicines agency
FDA: Food and drug administration
HL: Hodgkin lymphoma
MMAE: mono methyl auristatin E
Introduction

Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (ALCL) both express CD30, a cytokine receptor. Standard treatments for HL and systemic ALCL are effective for most patients, but relapse or refractory concern up to 30-40% for patients with advanced-stage HL [1]. The standard of care for patients with relapsed or refractory disease is high dose chemotherapy followed by autologous stem cell transplantation (ASCT), but these therapies are associated with frequent relapse (50%) [2]. For this group of patients, available options are limited [2].

CD30 is expressed on malignant Hodgkin Reed-Sternberg cells and in malignant cells of systemic ALCL, but has limited expression on healthy tissues [3]; it’s therefore an attractive target for innovative treatments. Brentuximab vedotin (BV) is a chimeric IgG1 directed against CD30 which is conjugated with an antimitotic agent, the mono methyl auristatin E (MMAE). After binding to CD30-expressing cell, the complex is internalized and the MMAE component is released intracellularly, causing disruption of microtubules and consequent apoptosis [4].

In 2012, BV has been approved by the US Food and Drug administration (FDA) and the European medicines agency (EMA) for the treatment of HL after failure of ASCT or at least two prior therapies for patients who are not candidate for ASCT, and for the treatment of systemic ALCL after failure of at least one prior therapy [5]. In 2016, regulatory authorities (FDA and EMA) extended the indication of BV to the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT [6]. In clinical studies, the most frequently adverse drug reactions (ADR) described with BV for the treatment of HL were peripheral sensory neuropathy, nausea, fatigue, neutropenia, diarrhea, pyrexia, vomiting, arthralgia, pruritus, myalgia, peripheral motor neuropathy, and alopecia [7]. However, post-authorization data are needed to confirm the safety profile [8]. Hence, the objective of this study was to assess the frequency and nature of significant ADR in patients treated with BV in a real-world setting.

Methods

We performed a single-center, observational, retrospective study in the university hospital of Montpellier, France. Patients who received at least one injection of BV between January 2009 and December 2016 were included. The list of patients was provided by the clinical oncology pharmacy unit. Dates and number of injections, dosage and type of chemotherapy regimen were recorded.
using the electronic chemotherapy prescribing system. For each patient, medical history, concomitant treatment medical reports, clinical and paraclinical data were collected using electronic patient record and significant ADR (excluding expected side effects related to chemotherapy treatments such as nausea, vomiting, neutropenia, fatigue, etc.) were searched. For each new identified ADR, a causality assessment was performed according to the French method for the causality assessment of ADR [9] and cases were recorded in the French pharmacovigilance database. An ADR was defined as severe if it refers to grade 3 to 5 of the common toxicity criteria of adverse events (CTCAE) version 4.

Results

Overall, 39 patients received at least one injection of BV between January 2009 and December 2016. Median age was 43.2 years (min. – max.: 14.1 – 82.7) and 53.8% were males. The indication of BV was refractory or relapse HL for 30 patients (76.9%) and systemic ALCL for 6 patients (15.4%). Three patients (7.7%) were treated by BV for other types of lymphoma. The median number of injection was 5 (min. – max.: 1 – 23). BV was used alone for 23 patients and used with a concomitant chemotherapy for 16 patients. Bendamustine was associated with BV in 12 patients (30.8%) and other chemotherapies used concomitantly with BV were: cisplatin, dacarbazine, doxorubicin, vinblastine, gemcitabine, and vinorelbine. Eleven patients (28.2%) underwent ASCT before BV treatment. Overall, 20 patients (51.3%) experienced at least one significant ADR: for grade 1-2 of the CTCAE, only nervous system disorders, skin disorders, hepatobiliary disorders and infections were studied; for grade 3 to 5 of the CTCAE all types of ADR were taken into account. In total, 24 reactions were reported: one patient had 4 ADR (infectious colitis, cytomegalovirus [CMV] infection, paralytic ileus and peripheral neuropathy) and another patient experienced 2 ADR (paralytic ileus and peripheral neuropathy). Twelve out of 24 ADR were considered severe (50%) (grade 3 to 5 of the CTCAE). The most frequently observed significant ADR was peripheral sensory neuropathy (Table 1). In 4 cases, BV was discontinued because of ADR and for 6 patients a dose reduction was done. Four out of 12 patients treated by the association BV-bendamustine experienced an ADR (including 4 CMV infections) and 8 out of 11 patients who underwent ACST before BV presented an ADR (including 2 CMV infections). No CMV was detected or searched for
patients with colitis or hepatitis. Previous chemotherapies according to the type of ADR are reported in Table 2.

Among all the cases, 7 (29.2%) were spontaneous reported to the referent pharmacovigilance centre (Annex 1) and one was notified to the manufacturer.

Discussion

We conducted a post approval study of brentuximab-related ADR. About half of patients treated by brentuximab vedotin showed at least one ADR and the most common effects were peripheral neuropathy (33.3%) and CMV infections (25%). However, we focused on significant uncommon ADR and did not report common side effects related to chemotherapy (nausea, vomiting, aplasia, etc.).

Concomitant and previous treatment should be taken into account. Recently, a safety signal was issued by regulatory authorities concerning an increased incidence of opportunistic infections (including herpes zoster, CMV and hepatitis B) after treatment with bendamustine [10]. Indeed, it has been shown that patients treated by bendamustine presented prolonged lymphocytopenia and low CD4-positive T-cell counts, for at least 7-9 months, which may increase the risk of opportunistic infections [11]. In our study, among the 6 patients who developed a CMV reactivation, 4 had a concomitant treatment with bendamustine and 1 patient had a prior chemotherapy with bendamustine in the 6 months before the reactivation. One patient with CMV reactivation did not receive bendamustine (either before or during BV treatment) and among the 4 patients with concomitant treatment with bendamustine and CMV reactivation, half did not have lymphopenia (data not shown). These data suggest a role of BV in CMV reactivation. CMV infections (as other herpes viruses infections) are more frequent in patients with hematological malignancies [12]. However, there is a potential link to the specific anti-CD30 effect of BV and CMV infection [13]. Bekiaris et al. [14] showed that NK cells protect secondary lymphoid tissue from CMV. Within the affected organ, CMV infection triggers morphological changes and a general reduction in cellularity due to excessive apoptosis. These conditions favor the up regulation of CD30 on the surface of NK cells, which explains that NK cells express high level of CD30 in CMV infection. It appeared that expression of CD30 integrates survival signals to NK cells that allow them to prevent viral spread and subsequent disintegration of secondary lymphoid tissue. Failure to express CD30 results in escape of virus and tissue integration. BV is an antibody drug...
conjugate directed to CD30. Its conjugate binds to cells which express CD30, of which NK cells, precluding the up regulation of CD30 expression and consequently prevent NK survival and secondary lymphoid tissue remodeling. Therefore, it can be proposed that the use of BV may selectively reactivate CMV infection and possibly other herpes viruses. Besides, because of the non-specific manifestations of CMV disease, its incidence is probably underestimated.

Our results are consistent with the literature. A literature review found peripheral neuropathy as the most clinically significant BV related toxicity [7]. In a small clinical trial, CMV viremia was reported in 5 out of 25 patients (20.0%) treated with BV [15]. In this study, concomitant treatments especially with bendamustine were not reported. CMV reactivations occurred in our center have been previously detailed [13]. Monitoring CMV viral load in asymptomatic individuals who are receiving BV may not be practicable in treatment centers but it is important for clinicians to be aware of the potential risk for CMV infection and screening should be systematic in individuals who develop signs or symptoms compatible with a CMV disease. In our study, in a case of CMV pneumonitis, the virus was isolated by PCR in the broncho-alveolar fluid but not in the blood. Indeed, it seems that tissue PCR has a better sensitivity and that negative blood PCR did not exclude a CMV disease [16,17].

In 10 cases, ADR led to BV discontinuation or dose reduction. In the summary of product characteristics, the manufacturer specifies the dose adjustments in case of neuropathy or neutropenia. No details are given for other type of adverse events, and the question of loss of chance of cure may arise.

Our results highlight the importance of systematic post approval pharmacovigilance studies. Indeed, only 29.2% of the ADR were spontaneous reported, that underlining again the importance of under-reporting in pharmacovigilance. Moreover, safety in pediatric population and in the elderly was not established through clinical trials [8]. A phase IV study would be useful to explore systematic CMV detection. A prospective monitoring would indeed represent the optimal practice for innovative molecule such as BV to better assess its safety profile and optimal management of ADR.

**Disclosure of interest**

Authors have no conflict of interest to declare
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[13] Tudesq JJ, Vincent L, Lebrun J, Hicheri Y, Gabellier L, Busetto T, et al. Cytomegalovirus infection with retinitis after brentuximab vedotin treatment for CD30+ lymphoma. OFID 2017 https://watermark.silverchair.com/ofx091.pdf?token=AQECACHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9 Cf3qfKAc485ysgAAaAqewgGqBkgkqhkiG9w0BBwagggGbMIIBlwIBADCCAZAGCSqGSlb3DQEHATAeBglghkgBZQMEAS4wEQMzMJzUoAf5B3XYyW6g4AgEgqIIBYf1Xht83hWq11Sj b1kzb1SBBA-5QodLBtw0YPOqHXctjAKlmbGSLT880MVgL0UjdZpaAQEo-nbYRYGHLBBSZ_8_XZPLIY6ke_QGNI4U- zYeQDK3Fm9wjOWxn7d3mSluHQIbzz_vUPks63WEkXTaOFI_PPL860Zd2H5Agnu_18FvF6u 1zMrJn7WYTPHdijCQH9yxFNhTvLjBLYLLyWa8RXGqY1Ys6Rk_bRBagi03y41DvndZnI7PXlqLgf I2A3LIAQ67pfNDlbw0LQA-XKFXzGx9UCL5gzEtXJDOSzeofq7lwdo4zzE972xzXimmrFeTjT1rR-_wRERmvsoip7HDBnVHLdEtPojjooQdQ-5UFbrt-m_wFuSrD0brfRUFRFoK5W4GCXHqjjeIRX3AcUH98_g8Gsnze8fs6k2aCN-rKLHY8ujVdBW1VhVkp9LgUSBew8KTqPomAVjNNmy1penGzOk [Accessed 10 July 2018 (3 pp.)]


Table 1. Adverse drug reactions (ADR) occurring in patients treated by brentuximab vedotin

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All ADR (n = 24)</th>
<th>Severe ADR (CTCAE grade 3 to 5) [n = 12]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>8</td>
<td>33.3</td>
</tr>
<tr>
<td>CMV infection</td>
<td>6</td>
<td>25.0</td>
</tr>
<tr>
<td>Paralytic ileus</td>
<td>3</td>
<td>12.5</td>
</tr>
<tr>
<td>Infectious colitis</td>
<td>3</td>
<td>12.5</td>
</tr>
<tr>
<td>Cholestatic hepatitis</td>
<td>1</td>
<td>4.2</td>
</tr>
<tr>
<td>Skin reaction</td>
<td>1</td>
<td>4.2</td>
</tr>
<tr>
<td>Shock, unspecified</td>
<td>1</td>
<td>4.2</td>
</tr>
<tr>
<td>Zona</td>
<td>1</td>
<td>4.2</td>
</tr>
</tbody>
</table>

CMV: cytomegalovirus; CTCAE: common toxicity criteria of adverse events
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Peripheral sensory neuropathy (n = 8)</th>
<th>CMV infection (n = 6)</th>
<th>Paralytic ileus (n = 3)</th>
<th>Infectious colitis (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrogen mustards (n = 11)</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Nitrosoureas (n = 6)</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Platinum salts (n = 7)</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other alkylation agents (n = 4)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cytotoxic antibiotics (n = 4)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pyrimidine analog (n = 10)</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Purine analog (n = 2)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Anthracyclines (n = 11)</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Topoisomerase II inhibitors (n = 10)</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Miscellaneous (n = 2)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Monoclonal antibodies (n = 3)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vinca-alkaloids (n = 10)</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

BV: brentuximab vedotin; CMV: cytomegalovirus