

Cytomegalovirus Infection With Retinitis After Brentuximab Vedotin Treatment for CD30⁺ Lymphoma

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Brentuximab vedotin is an antibody-conjugated chemotherapy targeting CD30 indicated in treatment of several lymphomas. We report the first 3 cases of cytomegalovirus severe infections with retinitis following this treatment. Evolution was favorable, but relapse occurred after treatment rechallenge. We suggest vigilance about cytomegalovirus in patients treated with brentuximab vedotin.

Keywords. brentuximab vedotin; cytomegalovirus; Hodgkin's lymphoma; retinitis.

Cluster of differentiation 30 (CD30) is expressed by Hodgkin's lymphoma (HL) and anaplastic large T-cell lymphoma (ALCL) tumor cells [1], and therefore therapies have been developed to target it. Brentuximab vedotin (BV) is a chimeric immunoglobulin G1 directed against CD30 and conjugated with a cytostatic agent (mono-methyl-auristatin E) and triggers selective CD30⁺ cell death [2]. After accelerated US Food and Drug Administration approval in 2011 [3], BV was registered for the treatment of relapsed/refractory ALCL and relapsed/refractory CD30⁺ HL. CD30 is a trans-membrane glycoprotein that belongs to the tumor necrosis factor receptor (TNFR) superfamily. It is normally expressed on activated B, T, and natural killer (NK) cells [1]. This receptor is involved in primary CD8⁺ T-cell expansion [4] and in terminating cytotoxic response and homing [5]. CD30–CD30 ligand (CD30L) interaction takes a critical place

in the cross-talk between immature dendritic cells (iDCs) and NK cells, leading to NK-cell activation and iDC maturation [6].

Here we report 3 cases of severe cytomegalovirus (CMV) infection including retinitis that occurred among 32 patients treated with BV between 2011 and June 2016.

PATIENTS

An 83-year-old man with a history of bronchiectasis, recurrent pneumonia, and *Aspergillus fumigatus* epiglottitis and seropositive to CMV immunoglobulin G (IgG) was treated for a stage IV HL (mixed-cellularity type, CD30⁺). He successively received 1 cycle of ABVD (adriamycin, bleomycin, vinblastin, dacarbazine), stopped for toxicity (deep neutropenia and right ankle arthritis), and then completed 5 cycles of mini-CHOP (cyclophosphamide, adriamycin, vincristine, prednisone), leading to partial response. A complete response was obtained after 6 cycles of MOPP (mustargen, vincristine, procarbazine, prednisone). The patient relapsed 3 months after and received BV at 75% of standard dose (ie, 1.35 mg/kg), every 3 weeks. The patient did not receive antiviral prophylaxis and did not undergo plasma CMV polymerase chain reaction (PCR) monitoring. Thirteen days after the third cycle, he experienced left vision loss. Left eye retinitis was diagnosed, with positive CMV PCR in aqueous humor. Plasma CMV PCR was positive (threshold of <500 copies/mL). According to guidelines [7], the patient received ganciclovir treatment (10 mg/kg/d) for 2 weeks, followed by valganciclovir (1800 mg/d for 7 days and then 900 mg/d), which led to clinical remission. A fourth BV cycle was administered 4 weeks after the diagnosis of retinitis. Two days after, a vision loss occurred, and recurrent left retinitis was confirmed. This relapse was effectively treated with valganciclovir (1800 mg/d), and BV was definitively stopped.

A 43-year-old man with no medical history who was seropositive for CMV IgG and who was suffering from stage IV HL (mixed-cellularity type, CD30⁺) received 3 cycles of VABEM (vinblastine, adriamycin, bleomycin, etoposide, methylprednisolone), leading to complete response. Relapse occurred 6.5 years later, and the patient received 2 cycles of DHAC (dexamethasone, cytarabine, carboplatine). Disease progressed, and he received successively 4 cycles of BV, followed by 5 cycles of GVD (gemcitabine, vinorelbine, doxil) plus BV, and finally 4 cycles of bendamustine plus BV, leading to complete response. The patient did not receive antiviral prophylaxis and did not undergo plasma CMV PCR monitoring. Twenty days after the fourth cycle (12 months after the first infusion of BV), he presented left vision loss. Symptoms grew progressively for 9 days until a left necrotic and hemorrhagic chorio-retinitis was

Received 27 February 2017; editorial decision 27 April 2017; accepted 3 May 2017.

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DOI: 10.1093/ofid/ofx091

diagnosed (Figure 1A). CMV DNA was found in plasma and vitreous humor. Moderate cytolysis and cholestasis (3× upper limit of the norm [ULN]) suggested hepatic involvement, but no biopsy was done. According to guidelines [7], treatment consisted of intravitreal and intravenous ganciclovir (10 mg/kg/d). Toxic neutropenia led to a switch to foscarnet (120 mg/kg/d) for 3 weeks, followed by valganciclovir (900 mg/d) at neutrophil recovery. Evolution was favorable, allowing autologous hematopoietic stem cell transplantation under foscarnet maintenance (60 mg/kg/d) without CMV reactivation. Brentuximab vedotin therapy was challenged again for an early relapse without CMV reactivation under foscarnet maintenance (follow-up: 8 weeks).

A 44-year-old man with no medical history who was seropositive for CMV IgG was treated for a stage IV peripheral CD30⁺ T-cell lymphoma (not otherwise specified). He received 4 cycles of CHOEP (CHOP plus etoposide) and then progressed. He successively received 2 cycles of DHAC, 3 cycles of bendamustine, and 1 cycle of CEP (cyclophosphamide, etoposide, prednisone). The patient did not receive antiviral prophylaxis and did not undergo plasma CMV PCR prophylaxis. Finally, BV therapy was started, and 2 weeks after the second cycle, a febrile dyspnea led to a diagnosis of systemic CMV disease, with blood CMV PCR strongly positive (6.03 log copies/mL); hepatitis

(Alanine-Amino-Transferase: 9.5× ULN, Gamma-Glutamyl-Transferase: 33× ULN); and putative pneumonia (CMV PCR-positive on expectorations and computed tomography scan ground-glass opacities) (Figure 1B). According to guidelines [7], antiviral treatment by valganciclovir (1800 mg/d) was started, and the third course of BV was administered. Despite treatment, plasma CMV PCR remained positive after 3 weeks, leading to a switch to foscarnet. The fourth BV cycle was infused. This treatment was marked by a septic shock with multiple putative origins (colitis, pneumonia, catheter-related bacteremia). In a context of renal toxicity, a combination therapy of half of a dose of foscarnet and half of a dose of ganciclovir was then successfully administered for 6 weeks. One month later (4 months after the first diagnosis of CMV reactivation), a rapidly progressive bilateral vision loss led to a diagnosis of bilateral retinitis. Plasma CMV PCR was positive (4990 copies/mL). Cytomegalovirus genotyping showed no mutation of resistance. No vitreal sampling was collected. Bilateral intravitreal ganciclovir and intravenous ganciclovir (10 mg/kg/d for 7 days) was administered, followed by valganciclovir (1800 mg/d for 14 days and 900 mg/d after), and antitumoral therapy was definitively stopped. Retinitis relapsed on the right eye 7 weeks later and was associated with mild viremia (743 copies/mL) despite maintenance treatment with oral valganciclovir. Treatment consisted of intravenous and twice-a-week intravitreal ganciclovir.

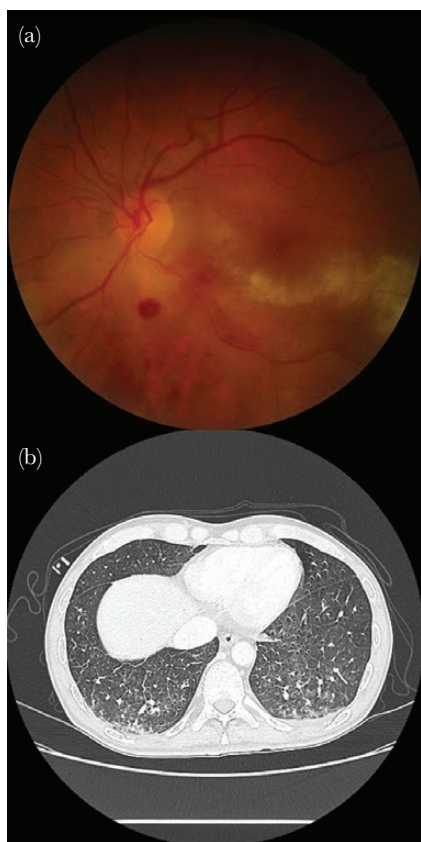


Figure 1. Paraclinical investigations in patients. A, Fundus examination of patient 2's left eye, showing inferior necrosis and hemorrhages. B, Thoracic computed tomography scan of patient 3, showing inferior bilateral ground-glass opacities.

DISCUSSION

This is the first report describing CMV retinitis after BV therapy for CD30⁺ lymphoma, highlighting an unknown adverse event of this drug. Despite a similar immunosuppression profile between our patients and those recruited for the pivotal studies [8, 9], no CMV reactivation was reported in those studies. However, CMV reactivation has been reported in 5 of 25 allogeneic hematopoietic stem cells transplantation (HSCT) recipients receiving BV therapy for relapse. Only 1 of these patients presented clinically significant organ involvement [10]. Because CMV reactivation is a frequent complication of allogeneic HSCT, we can hypothesize that HSCT was the determinant factor of those viremias.

The 3 patients depicted here had individual immunosuppression factors such as lymphoma and history of cytotoxic therapy, but none of them received allogeneic HSCT. Cytomegalovirus retinitis seems to be associated with deep immunosuppression conditions. In fact, in non-human immunodeficiency virus patients, most CMV retinitis occurs in solid-organ transplant or allogeneic HSCT recipients [11]. Outside the context of transplantation, only a few case reports of CMV retinitis have been reported in cancer patients, especially in HL or B-cell lymphomas [12]. Otherwise, if steroids are associated with more CMV reactivations [13, 14], BV therapy does not imply a change in the CS therapy of lymphoma patients. To our knowledge, no case report of CMV retinitis associated with T-cell lymphoma has been published.

CD30 is expressed on the surface of T cells and NK cells, and CD30L is expressed on the surface of iDC; these cells play a key role in antiviral response [15]. CD30 stimulation in activated memory T cells leads to interleukin 5 and interferon γ secretion [16]. Bekiaris et al showed that NK cells express a high level of CD30 in CMV infection [17]. CD30 seems therefore critical for anti-CMV response [18], maintaining effector and memory CD8⁺ T cells [4], inducing NK-cell survival, and preserving spleen white pulp architecture [17], which is required to support B-cell isotype switch and memory [19]. CD30-dependant iDC–NK cell cross-talk is involved in inflammatory cytokine secretion (tumor necrosis factor α , interferon γ , interleukin 6, interleukin 8) and T-cell proliferation [6]. Activated T cells express CD30, whose activation is involved in both terminating cytotoxicity and lymphocyte homing. Furthermore, soluble CD30 level has been associated with immune restoration inflammatory response after CMV retinitis in AIDS patients, which could underline its role in the retinal anti-CMV defense [20]. Hence, targeting CD30⁺ cells by BV is very likely to impair anti-CMV response also.

These cases illustrate the morbidity associated with CMV disease and especially retinal involvement in the context of BV therapy. They underline the potential role of BV therapy on anti-CMV immune response and indicate that new treatment with BV is unsafe without maintenance antiviral therapy. Ophthalmological examination and plasma CMV PCR should immediately be performed in patients suffering from visual loss in a context of BV therapy. For patients treated with BV after receiving multiple previous chemotherapies, physicians should be attentive to CMV reactivation and perform plasma PCR in respect to clinically or biologically relevant anomalies. Further studies to assess the incidence of CMV reactivation and the pertinence of prophylaxis in patients treated with BV are warranted.

Acknowledgment

Potential conflicts of interest. G. C. has served in a consultancy role with Roche and Celgene and has received honoraria from Gilead, Jansen, Roche, and Celgene. All other authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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