The Oncologist®

Letter to the Editor

HHV-8–Associated Multicentric Castleman's Disease in HIV-Negative Patient: A Novel Therapy for an Orphan Disease

MARIA M. SBENGHE,[a] EMMANUEL BESA,[a] AMIT MAHIPAL,[b] ALINA DULAU FLOREA,[a] PAUL BRAY,[a] JAIME CARO[a]

[a]Thomas Jefferson University, Philadelphia, Pennsylvania, USA; [b]Moffitt Cancer Center, Tampa, Florida, USA

Disclosures: Maria M. Sbenghe: None; **Emmanuel Besa:** None; **Amit Mahipal:** None; **Alina Dulau Florea:** None; **Paul Bray:** None; **Jaime Caro:** None.

Multicentric Castleman's disease (MCD) is a rare disease without a clearly defined treatment. Human herpesvirus (HHV)-8 and interleukin (IL)-6 have emerged as putative etiologic factors and therapeutic targets. We present the first case of MCD in an HIV^- $HHV\text{-}8^+$ patient who was successfully managed with concurrent bortezomib and ganciclovir.

A 43-year-old man presented in December 2009 with fever, night sweats, shortness of breath, weight loss, and enlarged lymph nodes. Physical examination revealed generalized lymphadenopathy and hepatosplenomegaly, which were confirmed by computed tomography (CT). His course in the hospital was complicated by hypotension, respiratory and renal failure, and severe anemia and thrombocytopenia. Serology for HIV-1 and HIV-2 and human T-lymphotropic virus (HTLV)-1 and HTLV-2 were negative, but he had a high HHV-8 viral load, 26,904 DNA copies/ml. A lymph node biopsy revealed HHV-8–associated MCD (Fig. 1A–1C). He was started on treatment with bortezomib, 1.3 mg/m^2 on days 1, 4, 8, and 11, together with ganciclovir. He had a dramatic clinical response after one cycle of therapy, with resolution of his respiratory and renal failure, normalization of his platelet count, and stabilization of his hemoglobin at ~10 g/dL. A repeat CT scan showed decreased lymphadenopathy and splenomegaly. He was maintained on bortezomib twice weekly, and then weekly because of the development of peripheral neuropathy, together with valganciclovir, 400 mg twice daily. He received two doses of tocilizumab, which he could not tolerate. He had a few clinical recurrences as a result of his noncompliance with either bortezomib or valganciclovir. His HHV-8 viral load was found to be elevated to 2.7 million DNA copies/mL on one of these occasions, but it then decreased to 246,000 copies/mL when valganciclovir was reinstituted and he went into clinical remission. His IL-6 levels varied in the range of 5–61 pg/dL and his HHV-8 viral load varied in the range of 1,000–10 million DNA copies/mL, but the IL-6 level and HHV-8 viral load did not parallel each other. He continued to show clinical benefit from the concurrent treatment with bortezomib and valganciclovir even 18 months after treatment was initiated.

There is no standard treatment for MCD. Limited courses of bortezomib have previously shown clinical benefit in three cases of $HHV\text{-}8^-$ MCD [1–3]. Its efficacy and safety in $HHV\text{-}8^+$ patients and as maintenance therapy have not been previously explored. The use of antiviral medications in the management of MCD was previously reported by Casper et al. [4, 5] in three HIV^+ patients, showing clinical improvement and clearance of HHV-8 viremia on treatment with ganciclovir and disease flares associated with the recurrence of HHV-8 viremia. Another patient, diagnosed with $HHV\text{-}8^+$ MCD 11 years after liver transplant, was successfully managed with valganciclovir and weaning off immunosuppression [6]. We used the combination of bortezomib and ganciclovir and achieved a very good initial clinical response, and we also observed stable disease as long as the patient was compliant with therapy. The use of bortezomib in this $HHV\text{-}8^+$ patient did not seem to worsen his outcome as long as the antiviral therapy was continued. Our case suggests that the concurrent use of bortezomib and ganciclovir in patients with HHV-8–associated MCD might have a synergistic effect, as bortezomib negatively inter-

Correspondence: Maria M. Sbenghe, M.D., Thomas Jefferson University, 1000 Walnut Street, Philadelphia, Pennsylvania 19107, USA. Telephone: 718-791-7127; Fax: 215-955-9641; e-mail: msbenghe@yahoo.com Received July 22, 2011; accepted for publication October 24, 2011. 1083-7159/2012/$40.00/0 http://dx.doi.org/10.1634/theoncologist.2011-0226

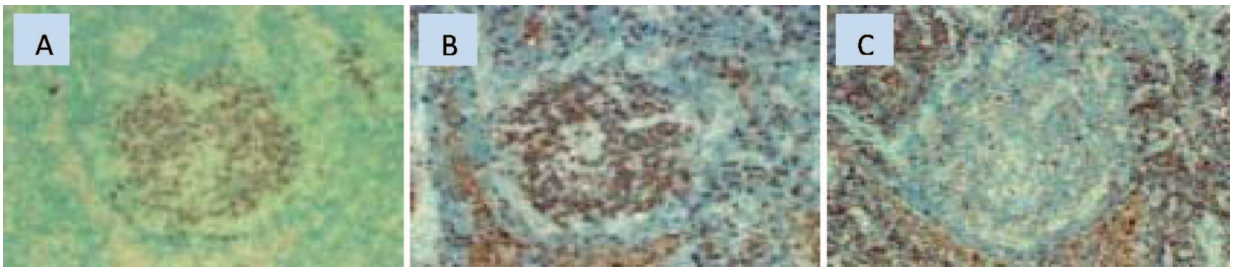

Figure 1. Section of axillary lymph node biopsy, immunostaining. **(A):** Human herpesvirus (HHV)-8–infected plasma cells and plasmablasts inside the germinal center; all infected cells show nuclear labeling for latency-associated nuclear antigen of HHV-8. **(B):** The same cells also stain for λ light chains. **(C):** There was an absence of staining for κ light chain of plasma cells inside the germinal center; interfollicular zone is expanded by polytypic plasma cell proliferation.

feres with IL-6 production and antiviral therapy controls the viral replication and inflammatory and proliferative response associated with viral IL-6 [7]. We believe that the concurrent use of bortezomib and ganciclovir is an acceptable initial therapy for patients with MCD presenting with multiple organ failure not able to tolerate more aggressive chemotherapy and also in patients intolerant to IL-6 inhibitors, and it can be used as maintenance therapy in patients showing stable disease on therapy. Our therapeutic approach, the concurrent use of bortezomib and ganciclovir or valganciclovir as initial and maintenance therapy, provided a long-term clinical benefit and deserves further exploration.

Author Contributions

Manuscript writing: Maria M. Sbenghe, Emmanuel Besa, Amit Mahipal, Alina Dulau Florea, Paul Bray, Jaime Caro

References

1. Yuan ZG, Dun XY, Li YH et al. Treatment of multicentric Castleman's disease accompanying multiple myeloma with bortezomib: A case report. J Hematol Oncol 2009;2:19.

2. Sobas MA, Alonso Vence N, Diaz Arias J et al. Efficacy of bortezomib in refractory form of multicentric Castleman disease associated to POEMS syndrome (MCD-POEMS variant). Ann Hematol 2010;89:217–219.

3. Hess G, Wagner V, Kreft A et al. Effects of bortezomib on pro-inflammatory cytokine levels and transfusion dependency in a patient with multicentric Castleman disease. Br J Haematol 2006; 134:544–545.

4. Casper C, Wald A. The use of antiviral drugs in the prevention and treatment of Kaposi sarcoma, multicentric Castleman disease and primary effusion lymphoma. Curr Top Microbiol Immunol 2007;312:289–307.

5. Casper C, Nichols WG, Huang ML et al. Remission of HHV-8 and HIV-associated multicentric Castleman disease with ganciclovir treatment. Blood 2004;103:1632–1634.

6. Lim EJ, Crowley P, Mitchell CA et al. Post-liver transplantation multicentric Castleman disease treated with valganciclovir and weaning of immunosuppression. Am J Transplant 2011;11: 169–172.

7. Neipel F, Albrecht JC, Ensser A et al. Human herpesvirus 8 encodes a homolog of interleukin-6. J Virol 1997;71:839–842.