bjh short report

Bortezomib in combination with infusional dose-adjusted EPOCH for the treatment of plasmablastic lymphoma

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Summary

Plasmablastic lymphoma (PBL) is a rare and aggressive CD20-negative lymphoma. Despite improvements of the biology behind PBL, it still represents a challenge from the diagnostic and therapeutic perspectives for pathologists and clinicians. PBL is characterized by high rates of relapse and short median survival with standard approaches. Here, we report the use of the combination of bortezomib and infusional etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (V-EPOCH) in three patients with PBL; two were HIV-positive and one was HIV-negative. All three patients obtained a durable complete response to V-EPOCH with survival times of 24, 18 and 12 months respectively.

Keywords: Plasmablastic lymphoma, bortezomib, EPOCH.

Plasmablastic lymphoma (PBL) is a rare, aggressive CD20-negative variant of diffuse large B-cell lymphoma (DLBCL) that was initially described in the oral cavity of human immunodeficiency virus (HIV) patients (Delecluse *et al*, 1997). More recently, PBL has been reported in other immunosuppressed individuals such as solid organ transplant patients as well as immunocompetent patients (Morscio *et al*, 2014). Regardless of immune status, there seems to be an association between PBL, EBV infection and *MYC* gene aberrations (Castillo & Reagan, 2011). Pathologically, PBL is characterized by lack of CD20 expression and expression of plasma cells markers such as CD38 and MUM-1/IRF-4, with a high proliferation index (Stein *et al*, 2008). The cell of origin of PBL is the plasmablast, an activated B-cell in the process of plasmacytic differentiation but that has not yet become a resting plasma cell. The prognosis of PBL is uniformly poor using traditional chemotherapy regimens with overall survival (OS) times of approximately 12 months (Castillo *et al*, 2012). Here, we present our experience with three patients with PBL treated with the combination of bortezomib and dose-adjusted EPOCH (etoposide, doxorubicin and vincristine along with bolus cyclophosphamide and prednisone).

Patient 1 is a 40-year-old man who presented with a three-month history of a progressively enlarging anal mass. He noted no pain secondary to the mass but did report positional pressure. His bowel movements had become more frequent and smaller secondary to the mass. He denied fevers, night sweats, or weight loss. Performance status was ECOG 0. Exam showed a large perianal mass of approximately 5 cm × 3 cm with no other palpable lesions (Fig 1, top). A positron emission tomography with computed tomography (PET-CT) scan revealed increased uptake on the pelvic mass, right tonsilar mass and inguinal/cervical adenopathy (Fig 1, bottom). Laboratory testing was significant for HIV seropositivity with CD4 count of 290 cells/mm^3. LDH was 166 IU/dl. Diagnostic biopsy revealed a diffuse population of medium to large lymphoid cells with round to slightly irregular nuclei. The malignant cells were positive for expression of CD38 and IRF-4/MUM-1. MYC was variably positive (60% in highest regions). Immunostains showed KI-67 of 100%. CD20, CD19, PAX5, CD30, CD138 and human herpesvirus 8 (HHV-8) latency-associated nuclear antigen (LANA) were negative. EBER *in situ* hybridization and EBV PCR testing were positive. Immunohistochemical profile is shown in Fig 2. Fluorescent *in situ* hybridization (FISH) showed gain of *MYC* but no *MYC* gene rearrangement. His bone marrow was uninvolved. Taken together, the pathological and clinical diagnosis was most consistent with stage IV HIV-associated PBL.

Patient 2 is a 36 year-old man who initially presented to the hospital with painful draining nodules on his buttocks.

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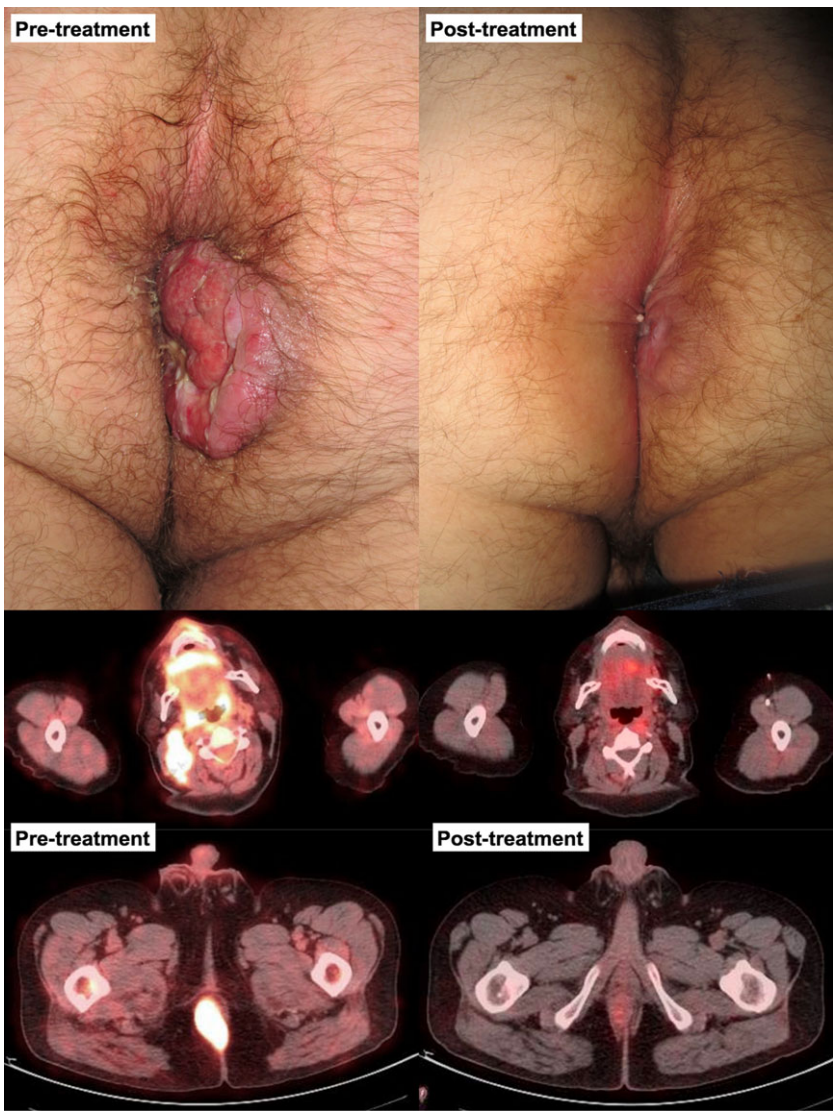

Fig 1. The upper panel shows a large perianal lesion before therapy with V-EPOCH (left), and post-treatment complete resolution (right). The lower panel shows increased 18F-FDG uptake in the right retropharyngeal and perirectal areas before therapy (left), and post-treatment lack of 18F-FDG uptake (right).

The nodules were first noticed 2 weeks before presentation, gradually increased in size, became painful, and developed a malodorous scent. The patient denied fevers, night sweats, or weight loss. Performance status was ECOG 0. On exam, a 3–4 cm mass on the right buttock was noted to be draining serous fluid while a large right-sided mass was identified on digital rectal examination. Initial laboratory evaluation was significant for a positive HIV test, CD4 count of 34 cells/mm^3, and LDH of 203 IU/dl. CT scan of abdomen and pelvis disclosed 16 cm × 9 cm × 8 cm solid mass with fistulous tracts to buttocks. CT scan of the chest showed 2·6 and 0·7 cm right upper lobe nodules. Biopsy of the mass showed large neoplastic cells with round to slightly irregular nuclei. The malignant cells were positive for KI-67 (90–100%), CD138 and IRF-4/MUM-1 while expression of CD20, CD19, PAX5, CD45, CD30 and HHV-8 LANA were negative. EBER *in situ* hybridization and PCR for EBV were positive. Molecular studies were also positive for immunoglobulin heavy chain gene rearrangement. His bone marrow was uninvolved. The above diagnosis was considered consistent with stage IV HIV-associated PBL.

Patient 3 is a 66 year-old male gastroenterologist with history of diverticulitis who presented with a 2-week course of worsening left lower quadrant abdominal pain, hematochezia and constipation. After a failed trial of antibiotics, the patient decided to self-scope, and found a 5-cm non-obstructive (75% stenosis) sigmoid mass located 25 cm from the anal verge. There were no fevers, night sweats or weight loss. Performance status was ECOG 0. CT scans did not reveal additional areas of involvement. The patient underwent a left hemicolectomy from the splenic flexure to the rectosigmoid junction. The pathology examination of the mass and six out of 21 lymph nodes revealed diffuse involvement by large cells with round nuclei. The malignant cells were negative for CD19 and CD20 but positive for CD138 and MUM-1/IRF-4. KI-67 expression was >90%. MYC was expressed in 15% of malignant cells. HIV ELISA was negative and bone marrow was uninvolved. The final diagnosis was stage II PBL in an

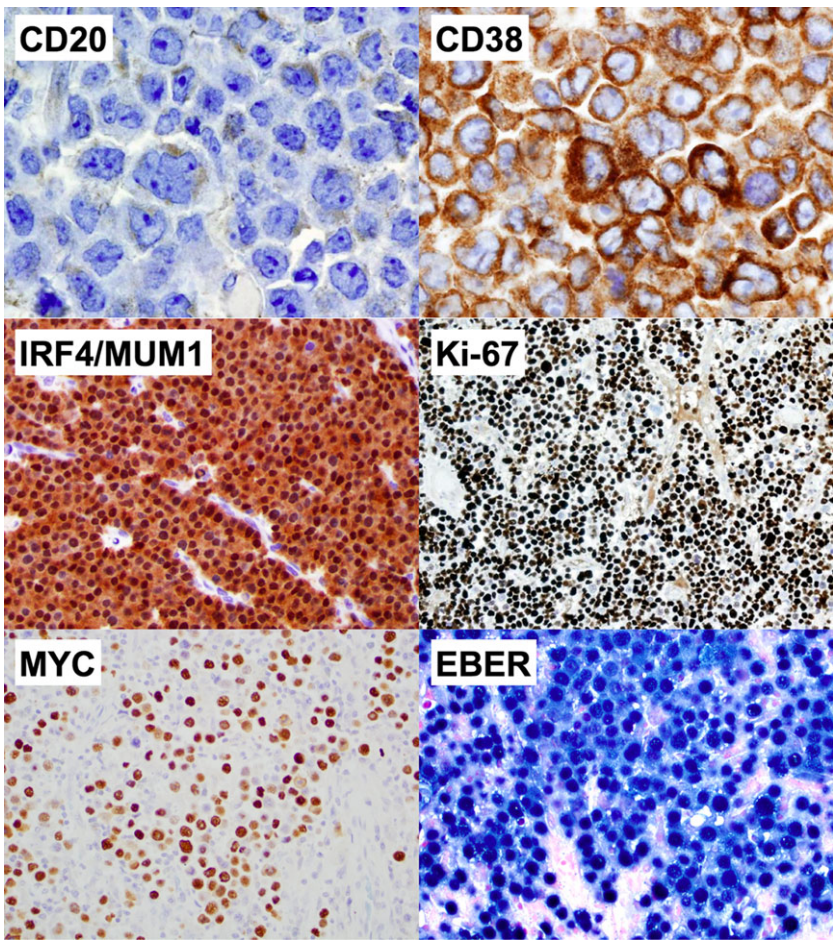

Fig 2. The pathological profile of a patient with HIV-associated PBL is shown here. The malignant cells did not express CD20 but were strongly positive for the plasma cells markers CD38 and IRF-4/MUM-1. The proliferation index was high with KI-67 expression of almost 100%. MYC expression was seen in approximately 60% of the malignant cells. EBER *in situ* hybridization shows active EBV infection in the malignant cells.

HIV-negative, otherwise immunocompetent individual. PET/CT performed after surgery but before initiation of therapy showed no areas of increased FDG avidity.

Each patient was initiated on dose-adjusted EPOCH in combination with bortezomib at a dose of 1·3 mg/m^2 administered subcutaneously (SQ) on days 1, 4, 8 and 11 on a 21-d cycle (V-EPOCH). Supportive therapy consisted on daily acyclovir 400 mg PO twice daily or valacyclovir 1000 mg PO once daily for herpes zoster prophylaxis, double-strength trimethoprim/sulfamethoxazole PO once daily three times a week or dapsone 100 mg PO once daily for *Pneumocystis carinii* prophylaxis, and pegfilgrastim 6 mg SQ on day 6 of V-EPOCH. Intrathecal liposomal cytarabine 50 mg was administered on day 2 of each cycle. Prior to intrathecal injection, 5–10 cc of cerebrospinal fluid was obtained and submitted for flow cytometry analysis.

Patients 1 and 3 developed grade 4 thrombocytopenia, which prompted holding of bortezomib on day 11 of each cycle. Patient 1 experienced herpes zoster reactivation following 3rd cycle of V-EPOCH, despite prophylaxis, likely associated with non-compliance. Patient 2 developed grade 2 peripheral neuropathy and prolonged thrombocytopenia during his 5th treatment cycle. Patient 3 developed small bowel obstruction after second cycle of V-EPOCH, which prompted continuation of therapy without vincristine. Both HIV-positive patients received combination antiretroviral therapy with efavirenz, emtricitabine and tenofovir concurrently with V-EPOCH. A dramatic reduction in tumour size was seen in both HIV-positive individuals following treatment (Fig 1). Patients 1 and 3 completed 6 total cycles of therapy. Patient 2 completed 5 cycles of V-EPOCH. Additional cycles were held for thrombocytopenia and neuropathy, which resolved after holding therapy. All patients showed complete resolution of FDG avidity by PET scans at the end of treatment (Fig 1). Monitoring with serial CT scans every 3 months was instituted. Currently, the disease-free survival times for patients 1, 2 and 3 are 24, 18 and 12 months respectively. All patients were referred for consolidative high-dose chemotherapy with autologous stem cell rescue (ASCT) in first remission, but declined. No patient has required additional treatment beyond V-EPOCH.

Here, we report three patients with a pathological diagnosis of PBL, two HIV-positive patients and one HIV-negative apparently immunocompetent patient, treated with frontline V-EPOCH. Patients attained a complete response and remain disease-free after therapy completion with relatively acceptable

short-term toxicity but no long-term toxicity. Given the poor outcomes of PBL with standard CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), the National Comprehensive Cancer Network recommendation is in favour of more intensive therapies such as EPOCH (Wilson *et al*, 2008). Infusional EPOCH is a reasonable option in patients with aggressive lymphomas with or without HIV infection. In a recent pooled analysis from over 1500 patients with HIV infection, the use of infusional EPOCH appeared associated with better outcomes (Barta *et al*, 2012). Currently, the Cancer and Leukaemia Group B is studying, in a randomized controlled study, rituximab in combination with either CHOP or EPOCH in patients with DLBCL with built-in molecular profiling (NCT00118209). Also, the National Cancer Institute is evaluating EPOCH in patients with MYC-positive DLBCL, for which patients with PBL are also eligible (NCT01092182).

The proteasome inhibitor bortezomib has shown to be highly active in myeloma, for which it is approved in Europe and the United States. Bortezomib has shown preclinical and clinical activity in other CD20-negative lymphomas such as primary effusion lymphoma (An *et al*, 2004; Sarosiek *et al*, 2010). Bortezomib also showed efficacy specifically in patients with activated or post-germinal center B-cell DLBCL (Dunleavy *et al*, 2009), providing a rationale for its use in PBL. Past case reports cite transient responses using the proteasome inhibitor bortezomib alone and in combination with chemotherapy in PBL patients with relapsed disease (Bibas *et al*, 2010; Cao *et al*, 2014; Yan *et al*, 2014). We believe the V-EPOCH regimen provides the opportunity to improve the outcomes of patients with PBL, in whom the development of more effective therapies is desperately needed.

In conclusion, we present a report on the use of V-EPOCH in patients with PBL. This combination showed efficacy and a relatively acceptable toxicity profile. Our study carries obvious limitations such as its retrospective design and small sample size, but let this serve as a potential platform in order to develop multi-institutional prospective therapeutic studies aimed at positively affecting the outcomes of patients with CD20-negative lymphomas, who are unlikely to derive benefit from the addition of anti-CD20 monoclonal antibodies to chemotherapy.

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JJC designed the study. JJC, JLR, WMS and ESW provided medical care to the patients. JJC and JLR wrote the manuscript.

Disclosures

The authors have no conflict of interest to disclose.

References

An, J., Sun, Y., Fisher, M. & Rettig, M.B. (2004) Antitumor effects of bortezomib (PS-341) on primary effusion lymphomas. *Leukemia*, **18**, 1699–1704.

Barta, S.K., Lee, J.Y., Kaplan, L.D., Noy, A. & Sparano, J.A. (2012) Pooled analysis of AIDS malignancy consortium trials evaluating rituximab plus CHOP or infusional EPOCH chemotherapy in HIV-associated non-Hodgkin lymphoma. *Cancer*, **118**, 3977–3983.

Bibas, M., Grisetti, S., Alba, L., Picchi, G., Del Nonno, F. & Antinori, A. (2010) Patient with HIV-associated plasmablastic lymphoma responding to bortezomib alone and in combination with dexamethasone, gemcitabine, oxaliplatin, cytarabine, and pegfilgrastim chemotherapy and lenalidomide alone. *Journal of Clinical Oncology*, **28**, e704–e708.

Cao, C., Liu, T., Zhu, H., Wang, L., Kai, S. & Xiang, B. (2014) Bortezomib-contained chemotherapy and thalidomide combined with CHOP (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) play promising roles in plasmablastic lymphoma: a case report and literature review. *Clinical Lymphoma Myeloma and Leukemia*, **14**, e145–e150.

Castillo, J.J. & Reagan, J.L. (2011) Plasmablastic lymphoma: a systematic review. *The Scientific World Journal*, **11**, 687–696.

Castillo, J.J., Furman, M., Beltran, B.E., Bibas, M., Bower, M., Chen, W., Diez-Martin, J.L., Liu, J.J., Miranda, R.N., Montoto, S., Nanaji, N.M., Navarro, J.T., Seegmiller, A.C. & Vose, J.M. (2012) Human immunodeficiency virus-associated plasmablastic lymphoma: poor prognosis in the era of highly active antiretroviral therapy. *Cancer*, **118**, 5270–5277.

Delecluse, H.J., Anagnostopoulos, I., Dallenbach, F., Hummel, M., Marafioti, T., Schneider, U., Huhn, D., Schmidt-Westhausen, A., Reichart, P.A., Gross, U. & Stein, H. (1997) Plasmablastic lymphomas of the oral cavity: a new entity associated with the human immunodeficiency virus infection. *Blood*, **89**, 1413–1420.

Dunleavy, K., Pittaluga, S., Czuczman, M.S., Dave, S.S., Wright, G., Grant, N., Shovlin, M., Jaffe, E.S., Janik, J.E., Staudt, L.M. & Wilson, W.H. (2009) Differential efficacy of bortezomib plus chemotherapy within molecular subtypes of diffuse large B-cell lymphoma. *Blood*, **113**, 6069–6076.

Morscio, J., Dierickx, D., Nijs, J., Verhoef, G., Bittoun, E., Vanoeteren, X., Wlodarska, I., Sagaert, X. & Tousseyn, T. (2014) Clinicopathologic comparison of plasmablastic lymphoma in HIV-positive, immunocompetent, and post-transplant patients: single-center series of 25 cases and meta-analysis of 277 reported cases. *American Journal of Surgical Pathology*, **38**, 875–886.

Sarosiek, K.A., Cavallin, L.E., Bhatt, S., Toomey, N.L., Natkunam, Y., Blasini, W., Gentles, A.J., Ramos, J.C., Mesri, E.A. & Lossos, I.S. (2010) Efficacy of bortezomib in a direct xenograft model of primary effusion lymphoma. *Proceedings of the National Academy of Sciences of the United States of America*, **107**, 13069–13074.

Stein, H., Harris, N. & Campo, E. (2008) Plasmablastic lymphoma. In: WHO Classification of Tumours of the Haematopoietic and Lymphoid Tissues (ed. by S. Swerdlow, E. Campo & N. Harris *et al*), pp. 256–257. IARC, Lyon.

Wilson, W.H., Dunleavy, K., Pittaluga, S., Hegde, U., Grant, N., Steinberg, S.M., Raffeld, M., Gutierrez, M., Chabner, B.A., Staudt, L., Jaffe, E.S. & Janik, J.E. (2008) Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. *Journal of Clinical Oncology*, **26**, 2717–2724.

Yan, M., Dong, Z., Zhao, F., Chauncey, T., Deauna-Limayo, D., Wang-Rodriguez, J., Liu, D., Wang, H.Y. & Pilz, R. (2014) CD20-positive plasmablastic lymphoma with excellent response to bortezomib combined with rituximab. *European Journal of Haematology*, **93**, 77–80.