CASE REPORT

Durable complete remission with combination chemotherapy and bortezomib in HIV-associated plasmablastic lymphoma

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SUMMARY

Plasmablastic lymphoma (PBL) is an aggressive form of non-Hodgkin's lymphoma (NHL) classically seen in patients infected with the human immunodeficiency virus, but can also be seen in other immunocompromised states such as transplant recipients, autoimmune diseases and the elderly. PBL is generally associated with a poor prognosis despite chemotherapy. There is evidence supporting the use of bortezomib in combination with standard chemotherapy to achieve durable responses in patients with PBL. We describe a patient with acquired immunodeficiency syndrome who presented with rectal pain and bright red blood per rectum. He was diagnosed with stage IVA PBL with anorectal, nodal, calvarial and hepatic involvement. Along with highly active antiretroviral therapy, he was treated with six cycles of dose adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (DA-EPOCH) plus bortezomib resulting in durable complete remission 30 months after diagnosis.

BACKGROUND

The present case describes durable complete remission achieved using dose adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (DA-EPOCH) and bortezomib in a patient with AIDS-associated plasmablastic lymphoma (PBL). PBL is an aggressive form of NHL that is usually associated with a poor prognosis.¹ The median overall survival of HIV-associated PBL is reported to be 4–15 months.^{2,3} Given the rarity of PBL, there are no randomised controlled trials to compare available treatment options, and treatment decisions are based on case reports or series and retrospective analysis of outcomes. The positive response seen in this patient demonstrates the potential utility of DA-EPOCH along with bortezomib for HIV-associated PBL.

Case presentation

A 34-year-old African-American man with HIV infection presented with 2 months of throbbing rectal pain on defaecation. He also reported occasional bright red blood per rectum for the same duration. He denied abdominal pain, vomiting or diarrhoea but did report constipation. He denied fevers, sweats or weight loss. On presentation, he was afebrile with a respiratory rate of 18/min, heart rate of 82/min and a blood pressure of 146/90 mm

Hg. Physical exam was notable for right cervical and bilateral inguinal adenopathy. Examination of oral cavity was negative for masses, ulcers or thrush. Abdomen was soft without tenderness or guarding. The liver and spleen were not palpable. There was marked tenderness on rectal examination. No rashes were noted. Medical history was notable only for HIV diagnosed at age 21. He had been off antiretroviral therapy (ART) for 4 years prior to presentation. He had a 3.75 pack-year smoking history and had quit smoking 6 years prior. He reported occasional alcohol use. He denied use of recreational drugs. Family history was notable for an unknown cancer in his aunt. There was no history of inflammatory bowel disease in the family.

Investigations

Laboratory studies were notable for a low haemoglobin of 11.7 g/dL (reference range 13.2–16.9 g/dL), an elevated lactate dehydrogenase (LD) of 990 units/L (reference range 135–225 units/L) and a low CD4 count of 209 cells/ μ L (reference range 530–1300 cells/ μ L). CT scan of the abdomen and pelvis revealed a circumferential 8×6.5×8.4 cm heterogenous mass involving the rectum and anus with no drainable fluid collection or obstruction (figure 1). He underwent a colonoscopy and was found to have a large anorectal mass which was biopsied. Histology revealed sheets of large pleomorphic cells with round to irregular nuclei, stippled to moderately coarse chromatin and moderate to abundant amount of amphophilic cytoplasm with frequent apoptotic bodies and scattered mitoses. Immunohistochemistry revealed lymphoma cells that were positive for CD138, multiple myeloma oncogene-1 (MUM-1) and Epstein-Barr encoding region (EBER), focally positive for CD79a and had a Ki-67 of 100%. Tumour cells were negative for human herpes virus 8 (HHV8) latency-associated nuclear antigen (LANA-1) and CD20.

Fluorescence in situ hybridisation (FISH) showed evidence of MYC/IGH gene rearrangement in 90.5% of tumour cells consistent with a t(8;14) translocation. FISH for B-cell lymphoma (BCL)-6 gene rearrangement or deletion or IGH/BCL2 translocation were negative.

Staging CT scans revealed innumerable axillary, supraclavicular, presacral and perirectal lymph nodes, innumerable small pulmonary nodules and a 1.5 cm liver lesion. MRI brain revealed a large

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Figure 1 (A) CT scan of the pelvis demonstrating the anorectal mass prior to initiation of chemotherapy. (B) Resolution of the mass after six cycles of therapy with dose adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin and bortezomib.

destructive right calvarial lesion with epidural component resulting in midline shift (figure 2). PCR testing for Epstein Barr virus (EBV) revealed 64 600 copies of EBV DNA per mL in his blood. Bone marrow biopsy showed no evidence of lymphoma. Lumbar puncture was not performed at diagnosis due to concern for raised intracranial pressure from the calvarial lesion. He was diagnosed with stage IVA plasmablastic lymphoma based on diffuse nodal and extranodal disease in the absence of fevers, sweats or weight loss.

Treatment

He was initiated on highly active antiretroviral therapy (HAART) with dolutegravir and emtricitabine-tenofovir. He underwent

Figure 2 (A) MRI brain demonstrating a destructive right frontotemporoparietal calvarial lesion with cortical erosion, subgaleal and large epidural components, causing moderate mass effect and leftward shift of midline structures. (B) Resolution of the right frontoparietal convexity mass after whole brain radiation therapy and six cycles of chemotherapy.

whole brain radiotherapy (2000 cGy in five fractions) for the extradural lymphoma. He subsequently underwent chemotherapy with standard doses of DA-EPOCH plus bortezomib (1.3 mg/m² on days 1, 4, 8 and 11) every 21 days for a total of six cycles. He received all planned doses of bortezomib. His maximum cyclophosphamide dose was 562 mg/m². He received five (out of eight planned) doses of intrathecal methotrexate (12 mg each) during cycles 2–6 for central nervous system prophylaxis, per his preference.

The patients' symptoms of rectal pain and bleeding had completely resolved after cycle 1. He experienced nausea during chemotherapy which was managed symptomatically.

Repeat CT scans after cycle 4 demonstrated dramatic decrease in size of pulmonary nodules, lymph nodes and the anorectal mass.

Imaging after completion of the six cycles demonstrated complete resolution of pulmonary nodules, adenopathy and the anorectal mass (figure 1). Repeat MR of the brain after completion of chemotherapy showed resolution of the calvarial mass and no evidence of brain parenchymal involvement (figure 2).

OUTCOME AND FOLLOW-UP

Patient is currently in complete and sustained remission at 30 months since his diagnosis with no evidence of disease. He continues to receive HAART. His CD4 count reached a nadir of 167 cells/μL about 1 month after completion of the sixth cycle of chemotherapy, but has been steadily rising since then with a most recent value of 520 cells/μL. His most recent LD is 181 units/L. The EBV viral load has not been repeated since his initial presentation.

After achievement of remission, he had been referred for autologous stem cell transplantation but he declined any further work up. He is undergoing clinical follow-up every 6 months.

Discussion

NHL is one of the three AIDS-defining cancers; PBL is a rare and aggressive subtype of NHL that is commonly seen in association with HIV/AIDS but can also arise in other immunocompromised states such as organ transplantation, autoimmune diseases and older age and rarely in immunocompetent patients as well.¹ There is a distinct male predominance and patients with HIV infection tend to be diagnosed at a younger age than those without.⁴ The cell of origin is believed to be a postgerminal centre B-cell or plasmablast. PBL cells usually do not express the pan-B cell marker CD20 but do express plasmacytic markers such as CD38, CD138, MUM-1 or CD79a.⁵ Myc gene rearrangements as well as EBV infection have been identified as important factors in the pathogenesis of PBL.¹ This patient's cancer did not express HHV-8 LANA1, the presence of which could have indicated extracavitary primary effusion lymphoma. A rare differential also included anaplastic lymphoma kinase (ALK)+diffuse large BCL; ALK testing was not performed in this patient.

Most common presenting symptoms include abdominal complaints (diarrhoea, haematochezia, pain) and localised masses or oral/nasal symptoms (ulcer, epistaxis, rhinorrhoea, sinusitis). Nodal involvement is seen in majority of patients, but extranodal involvement is relatively common.⁶

PBL is generally associated with an extremely poor prognosis despite chemotherapy, with median overall survival reported between 4 and 32 months.^{2–4 7 8} The guidelines from the National Comprehensive Cancer Network (NCCN) recommend that cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)-based regimens are not adequate therapy.

NCCN-recommended regimens include cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide and high-dose cytarabine (CODOX-M/IVAC), hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (hyperCVAD) or DA-EPOCH.⁹

Localised disease, use of chemotherapy and achievement of complete remission are associated with favourable prognosis. Patients with HIV have been reported to have improved outcomes compared with those without.⁴ Use of ART is recommended for all patients with HIV undergoing treatment for PBL.¹⁰

The present report describes complete remission obtained using DA-EPOCH along with bortezomib for HIV-associated stage IVA PBL. The patient experienced relatively acceptable short-term toxicity and no appreciable long-term toxicity. He remains in remission at 30 months after diagnosis and is adherent to ART.

Bortezomib is a proteasome inhibitor that is approved for use in myeloma, with which PBL has immunophenotypic similarity. It has been used in other forms of NHL as well.^{11 12} Bortezomib has been combined with different multiagent chemotherapy regimens for use in both HIV associated and non-HIV associated PBL, with promising results.^{2 13–27} Of these, Castillo *et al* have also described use of bortezomib in combination with EPOCH to achieve sustained remission in two HIV-associated cases of PBL without significant toxicity.²⁵

PBL accounts for approximately 2% of AIDS-related lymphomas, and it is unlikely that there will be a large-scale randomised trial to evaluate therapeutic options.¹⁰ There is mounting evidence that addition of bortezomib to EPOCH is safe. Hence, in the absence of contraindications, addition of bortezomib to standard DA-EPOCH could be discussed with patients and offered as a therapeutic option.

Learning points

- Plasmablastic lymphoma is an aggressive form of non-Hodgkin's lymphoma commonly seen in patients infected with HIV but can be seen in immunocompromised patients without HIV infection as well.
- It is generally associated with a poor prognosis despite standard therapy.
- This case report describes successful remission obtained in a patient with HIV-associated plasmablastic lymphoma using dose adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin+bortezomib therapy.

Contributors NA, AG and NS were involved in the conception and design, acquisition and analysis of data, drafting the article or revising it critically for important intellectual content and gave final approval of the version published.

Competing interests None declared.

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