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Case Report

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Plasmablastic Lymphoma of the Maxillary Sinus: Case Report of a Novel Treatment Approach of Concurrent Bortezomib and Intensity-Modulated Radiotherapy

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ABSTRACT

Plasmablastic lymphoma (PBL) is an aggressive variant of diffuse large B-cell lymphoma and was initially described as affecting the oral cavity of patients with HIV. Recently, it has been better characterized through histopathology and case reports demonstrating that it may affect HIV-negative patients as well. In particular, elderly patients that have immunosenescence can develop PBL, and it may present in anatomic sites outside the oral cavity. Treatment typically consists of aggressive chemotherapy regimens, such as CHOP, EPOCH, or hyper-CVAD; however, elderly patients may not be able to tolerate such intense regimens. We present a case of an elderly man with PBL of the maxillary sinus treated with a unique regimen of concurrent bortezomib and intensity-modulated radiotherapy (IMRT). This treatment produced a significant, durable tumor response and was well tolerated. Bortezomib with IMRT could be considered an alternative to more intense chemotherapy regimens, particularly in elderly patients with PBL, although prospective studies are needed to further test the safety and efficacy.

INTRODUCTION

Plasmablastic lymphoma (PBL) is a relatively new histopathologic variant of diffuse large B-cell lymphoma (DLBCL) and was initially described by Delecluse et al. in 1997 as presenting in the oral cavity of HIV-positive patients [1]. Since that initial description, PBL has been described more frequently in the literature, represented in case reports or small case series as occurring in HIV-negative patients and in anatomic sites outside of the oral cavity. HIV-negative patients tend to have an older age at presentation and a worse prognosis compared to HIV-positive patients. Within the smaller subset of HIV-negative patients, there are even more rare associations such as Epstein-Barr virus infection and other immunecompromised states such as solid organ transplantation and immunosenescence secondary to advanced age [2, 3, 4]. It also can occur in many anatomic sites, ranging from classic nodal sites to extra nodal sites, such as the gastrointestinal tract, soft tissues, and

paranasal sinuses [5].

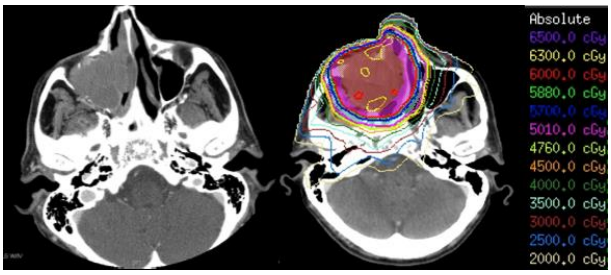
The major focus of the current literature has been on characterizing the clinicopathologic and epidemiologic features of this disease, using them to predict the outcomes of these patients. Much less attention has been given to the various treatment approaches used for the different clinical settings in which PBL can occur. There have been no prospective trials of therapy in PBL and, in fact, there is no standard therapy for the disease. Previously described treatment approaches seem to either focus on treating the underlying HIV infection with HAART therapy or using specific chemotherapy regimens. Chemotherapy options have consisted of traditional CHOP or CHOP-like regimens, though current NCCN guidelines recommend use of more intensive regimens like EPOCH or hyper CVAD, since PBL has a more aggressive clinical course than other types of DLBCL [6]. These current treatment approaches have little translation to the subset of HIV-negative elderly patients with PBL who may not tolerate or wish to pursue CHOP or intensive chemotherapy regimens. Specifically, the role and timing of radiotherapy has yet to be described.

Three recent case reports have reported the potential benefit of the proteasome inhibitor, bortezomib, in the treatment of PBL [7-9]. Bortezomib acts by blocking NF-kB and sensitizing PBL to cytotoxic chemotherapy ultimately inducing cell cycle arrest and apoptosis. To our knowledge, bortezomib has not been used in combination with local radiotherapy for the treatment of PBL. With this context, we present a case of an 87-year old, HIV-negative man with PBL of the maxillary sinus treated with a novel approach of induction bortezomib combined with consolidative local radiotherapy.

CASE REPORT

An 87-year old man with no major medical comorbidities presented with a 2-month history of right facial pain, swelling, intermittent epistaxis, and right nasal obstruction. On exam, he had a leftward deviating septum, complete obstruction of his right nare, and asymmetric appearance of the zygomatic bones with the right more prominent than left. CT with contrast revealed a large, aggressive appearing expansile mass in the right maxillary sinus with erosion superiorly into the inferior right orbit and right ethmoid air cells (fig. 1). The mass abutted the cribiform plate and obstructed the right frontal and sphenoid sinuses. Staging CT of the chest, abdomen, and pelvis revealed absence of other sites of disease.

Figure 1. CT at presentation (left) and isodose lines of external beam plan (right)



A flexible, fiberoptic nasoendoscopy exam was performed with fine needle aspiration biopsy of the mass at the level of the right middle meatus. Pathology demonstrated highly atypical cells that stained strongly for CD138, MUM-1, and EBER-1 (in situ hybridization test for EBV RNA). Furthermore, the cells were negative for B cell markers, such as CD20, CD79a, and PAX5 and also negative CD30, cytokeratins, S100, and PLAP. The cells were most consistent with EBV-positive plasmablastic lymphoma. Laboratory workup revealed negative HIV, normal serum protein electrophoresis, and uninvolved bone marrow. The patient was determined to have stage IE disease.

Due to the size of the lesion and local invasion into the right orbit and paranasal sinuses, the patient was deemed unresectable by the otolaryngology team with the recommendations to pursue chemotherapy and possibly radiation. Due to the patient's advanced age, aggressive cytotoxic chemotherapy was not recommended; instead, we pursued concurrent bortezomib and intensity-modulated radiotherapy (IMRT). Treatment with bortezomib at 1.3 mg/m^2 subcutaneously on days 1, 4, 8, 11 of a 21-day cycle was initiated with dexamethasone 40 mg on the day of and day after each bortezomib injection. There was an elapsed time of 23 days between the first bortezomib injection and the start of intensity modulated radiotherapy, consisting of two cycles.

The radiation plan consisted of an IMRT dose-painting technique to a dose of 50 Gy in 30 fractions (1.67 Gy per fraction) to the entire tumor, ipsilateral maxillary sinus, and partial contralateral nasal cavity. The gross tumor plus a small margin was treated to 60 Gy in 30 fractions (2 Gy per fraction). Because the extent of disease was confined to an

extranodal site, we elected not to cover regional lymph nodes. A total of six beams were used for target coverage (fig. 1).

Figure 2. CT scan at two weeks (left), and 3-month (right) after treatment

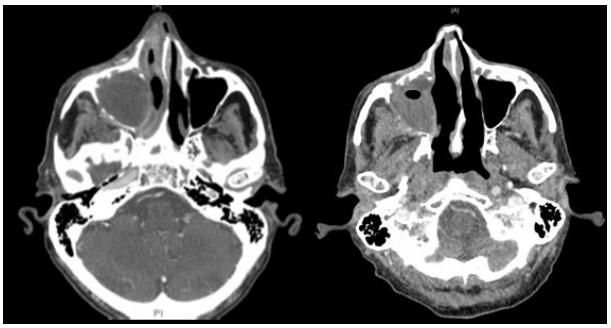
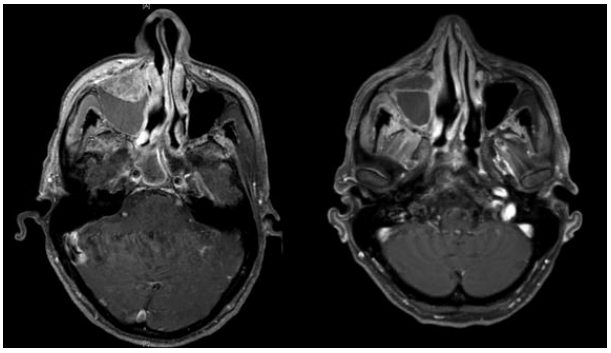


Figure 3. MRI with contrast prior to radiation (left) and 6 months post radiation (right).



The patient tolerated both the bortezomib and the radiation very well initially. He did not develop any significant hematologic or neuropathic side effects from bortezomib. The radiation was well tolerated with only grade II dermatitis in field, nasal passage dryness, sinus congestion, minor epistaxis and some mild keratopathy. There was no increased toxicity from radiation because of concurrent use with bortezomib. After 2 cycles and the start of radiation there was a reduction in the size of the maxillary sinus mass. Bortezomib was discontinued because of a clostridium difficile infection, and radiation was continued alone. After radiation, he received 2 consolidative cycles of bortezomib but ultimately this was discontinued because of unrelated cellulitis and fatigue. In total, he received four cycles of bortezomib. After 6 months of follow-up, the patient continued to do well clinically with persistent dry nasal passages and orbit; however, no evidence of disease on physical exam. Radiographically, he has had a great response with decreased size of the mass at 3-month follow-up (fig. 2) and only post-radiation change with no mass on MRI at 6-month follow-up (fig. 3). Last follow-up was one year and seven months post-treatment, and he continues to have no evidence of disease clinically and to have recovered well from the bortezomib and radiation with no chronic toxicities.

DISCUSSION

Since first being described in the literature in the late 1990's, plasmablastic lymphoma has evolved from a disease specifically affecting immunocompromised, HIV-positive patients to a disease affecting a larger group of patients, who are HIV-negative but still immunocompromised from a variety of causes. Falling into this latter category is the elderly population, who sometimes experience a compromise in their immune systems from immunosenescence, a multifactorial deterioration of the immune system secondary to the aging process.

The elderly, HIV-negative subset of patients with plasmablastic lymphoma represent a unique subset, whose treatment approach differs greatly from the classic HIV-positive patient or even younger patients, who may be able to tolerate more intensive cytotoxic therapy. Some elderly patients will not be able to tolerate traditional chemotherapy used for non-hodgkins lymphoma, such as R-CHOP or hyper-CVAD, and therefore require a different treatment approach that may be better tolerated.

Bortezomib is a small molecule proteasome inhibitor that was approved by the FDA in 2003 for the treatment of multiple myeloma and was recently approved for relapsed mantle cell lymphoma. It has been shown in pre-clinical studies to inhibit the pro-survival signal transcription factor nuclear factor-κB (NF-κB), which functions at the regulatory sites for many molecules that promote angiogenesis, advance progression through the cell cycle, and inhibit apoptosis in certain human malignancies [10]. NF-κB also causes dysfunction of the common tumor suppressor gene p53. Therefore, bortezomib may possibly sensitive cells to radiation and other forms of chemotherapy by inhibiting radiation-or chemo-induced NF-κB and enhance cell killing in many aggressive malignancies including recurrent head and neck squamous cell carcinomas. There is accumulating evidence for a potential role of bortezomib in non-germinal center DLBCL [11], and clinical trials are currently underway to further explore this. Bortezomib has

the ability to affect both plasma cells and B cells. For treatment of PBL, the available evidence is limited to case reports and has been shown to cause a dramatic clinical response and tumor lysis syndrome in plasmablastic lymphoma.

In a case report by Lipstein et al, an elderly, HIV-negative man with advanced PBL was initiated on rituximab, cyclophosphamide, and dexamethasone all on day 1 with bortezomib at 1.3 mg/m^2 on days 2, 5, 9, and 12. Within 1-2 days after his first bortezomib infusion, he was found to have clinical and laboratory evidence of tumor lysis syndrome. He was treated appropriately, and 2 weeks later, he had full resolution of all palpable sites of disease. He later succumbed to sepsis secondary to a urinary tract infection about 30 days after his first cycle [7].

Another case report by Bose et al describes a 42 year-old, HIV-positive man who was found to have an advanced PBL, involving bone and viscera. Given the HIV status, he was started on HAART and could not receive anthracycline-based chemo regimens because of persistent hyperbilirubinemia. He was initiated on bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11. A PET/CT performed 7 days after starting the bortezomib showed a dramatic response at all sites of disease. However, he ultimately succumbed to severe septic shock from multi-organism bacteremia [8].

A third case report by Bibas et al discusses a 19 year-old, HIV-positive man who presented with generalized lymphadenopathy and was ultimately diagnosed with stage IVB plasmablastic lymphoma. He progressed through intensified purging-free high dose chemotherapy and HAART therapy and subsequently began bortezomib 1.3 mg/m^2 and dexamethasone on days 1, 4, 8, and 11. He demonstrated mixed response to bortezomib and thus this regimen was continued with the addition of gemcitabine, oxaliplatin, cytarabine intrathecally, pegfilgrastim (GOVDD). He initially responded but later progressed and was placed on chemotherapy regimens not including bortezomib because of severe sensory motor polyneuropathy [9].

Our case is different compared to those above in that our patient had more advanced age, limited stage at presentation, and treatment included concurrent bortezomib with external beam radiation. In our patient, more emphasis was placed on local control given the only site of disease was the maxillary sinus. As such, there was less need to deliver aggressive chemotherapy as the case above, nor did we think he would tolerate a multi-drug cytotoxic regimen. Our treatment paradigm may not be as appropriate for patients' with extensive stage disease given the lack of feasible radiation targets.

Currently, the combination of bortezomib and external beam radiotherapy is the focus of several phase I/II studies to determine the safety and efficacy in the treatment of primary CNS, recurrent head and neck, and metastatic solid organ malignancies with or without cytoxic chemotherapy [10-13]. These studies have shown that the combination can be safely administered with minimum severe toxicity. The most common toxicity encountered is lymphopenia. Other more common minor side effects can include nausea, diarrhea, and fatigue. Given the positive early clinical data, the combination of bortezomib and radiation will be further investigated in a phase III design.

Since plasmablastic lymphoma has a fairly aggressive natural history, bortezomib alone is unlikely to produce improved control or cure compared with traditional CHOP or hyper CVAD regimens. With this understanding, external beam radiation was added to bortezomib to consolidate the tumor in the maxillary sinus, providing a well-tolerated alternative to additional chemotherapy. This case report is further evidence that the combination of bortezomib and radiation is well-tolerated and safe, particularly in the elderly population. The combination also was shown to produce quick and durable control of this locally aggressive head and neck lymphoma.

There are obvious limitations to this case report. The first being that our patient, although at an advanced age, was physically fit with few co-morbidities and may not represent the typical elderly patient. The second is that there is limited follow-up on this patient with only one year and seven months, which may impact our ability to assess the durability of local control. Lastly, bortezomib was used somewhat neoadjuvantly in this case as the radiation started after 5 doses of bortezomib, producing a great clinical response and reduction in size. After radiation started concurrently, there was further decrease in the size of the mass. Given the response to bortezomib

alone, radiation could possibly have been delayed for salvage if response to chemo was limited. Given the good health of the patient and the aggressive nature of the malignancy, it was felt that consolidative radiation would give extra local control benefit.

Because of the rarity of plasmablastic lymphoma in the elderly, it is not feasible to conduct large trials investigating the best therapeutic approach. The current literature focuses on the most common subset of HIV-positive patients with this cancer, which doesn't apply to the unique immunosenescent, elderly population, who cannot tolerate the intense chemotherapy traditionally given. This case is further evidence that a different treatment approach, bortezomib and consolidative radiation, in this subset of patients with limited disease stage of this rare malignancy is potentially well-tolerated, safe, and produces effective local control. Although further investigation is needed, this proposed regimen is a possible alternative treatment for plasmablastic lymphoma in patient populations that cannot tolerate more aggressive therapy.

CONFLICT OF INTEREST

None

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