



Invited review

Bortezomib in plasmablastic lymphoma: A glimpse of hope for a hard-to-treat disease



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ABSTRACT

Plasmablastic lymphoma (PBL) is a rare and hard to treat disease. With current standard chemotherapeutic regimens, PBL is associated with a median overall survival of 12–15 months. We performed a systematic review of the literature through March 31, 2017 looking for patients with a diagnosis of PBL who were treated with bortezomib, alone or in combination. We identified 21 patients, of which 11 received bortezomib in the frontline setting and 10 received bortezomib in the relapsed setting. Eleven patients were HIV-positive and 10 were HIV-negative. The overall response rate to bortezomib-containing regimens was 100% in the frontline setting and 90% in the relapsed setting. Furthermore, the 2-year overall survival of patients treated upfront was 55%, and the median OS in relapsed patients was 14 months. Although the sample size is small, we believe our results are encouraging and should serve as rationale to investigate bortezomib-based regimens in patients with PBL.

1. Introduction

Plasmablastic lymphoma (PBL) is a rare B-cell lymphoma with morphological, immunophenotypical and genomic features between aggressive large B-cell lymphomas and plasma cell neoplasms [1]. The vast majority of cases will express CD138, CD38, and IRF4/MUM1—plasma cell markers – and lack expression of typical B-cell markers such as CD19 or CD20. Given these distinct features, the WHO has categorized PBL as an aggressive subtype of diffuse large B-cell lymphoma (DLBCL) [2].

This rare subtype of DLBCL was originally found to be associated with HIV-infected patients [3,4]. However, cases of PBL have also been reported in patients with other immunodeficiencies and even in apparently immunocompetent patients [5]. Treating PBL represents a challenge given there is no standard regimen of treatment established for these patients. Currently, the National Comprehensive Cancer Network (NCCN) recommends against the use of standard cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), in favor of more intensive regimens [6]. We also need to have in mind that several patients with PBL are elderly and/or are immunosuppressed and might not benefit from intensive therapies [7]. However, the outcome of PBL patients remains poor, and novel approaches are warranted.

Amongst the therapeutic agents used to treat PBL, the proteasome inhibitor bortezomib alone or in combination has been associated with

promising results [8,9]. In this article, we present a systematic review of PBL cases treated with bortezomib-containing regimens, and describe response and survival outcomes on these patients.

2. Methods

2.1. Literature search

Two authors performed a literature search independently using PubMed through March 31, 2017. The key terms used in the search were: “plasmablastic lymphoma AND bortezomib”. The titles and abstracts were reviewed and full-text articles were selected based on our inclusion criteria. The reference list of each selected study was reviewed to search for additional studies.

2.2. Inclusion and exclusion criteria

An article was considered relevant if it contained original data from patient(s) older than 18 years of age with a pathological diagnosis of PBL treated with bortezomib alone or in combination. Case reports and retrospective and prospective case series were included in this review. Cases with ALK1 or HHV8 Latent Nuclear Antigen expression were excluded, as these markers are consistent with ALK-positive DLBCL and primary effusion lymphoma, respectively. Any discrepancies on

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inclusion or exclusion of a study were resolved through consensus in all cases. If there were multiple publications from the same study, only the most recent was selected, using the older publications only to clarify methodology or characteristics of the population.

2.3. Data gathering

The data extraction was performed independently by two authors, and included pertinent clinical (e.g. age, sex, stage, HIV status, etc.), pathological (e.g. CD20, CD38, EBER, etc.), treatment, response and overall survival (OS) data. For response assessment, we used the 2007 Cheson response criteria, whenever possible [10]. OS was defined as the time from PBL diagnosis and death or last follow-up, and was estimated using the Kaplan-Meier method for incomplete observations. Comparisons between groups were performed using the log-rank test. All calculations and graphs were obtained using STATA/SE 13.1 (StataCorp, College Station, TX).

3. Results

3.1. Patient characteristics

The literature search rendered 22 articles of which 9 articles were excluded; 4 were reviews, 3 reported on plasmablastic myeloma and 2 were pre-clinical. From the remaining 13 articles, a total of 21 patients met inclusion criteria and were included in this study [8,9,11–21]. Eleven patients received bortezomib-containing regimens in the frontline setting, and ten patients received bortezomib-containing regimens in the relapsed and/or refractory setting.

The patients' clinical characteristics are summarized in Table 1. The median age for the patients with frontline use of bortezomib was 42 years (range 34–80 years) and 50 years (range 19–66 years) in the relapsed group. There was a male predominance in both groups, 10 (91%) in the frontline, and 9 (90%) in the relapsed group. Eleven patients (52%) were HIV-positive. Sixteen patients (76%) had advance disease by Lugano staging criteria. All cases had extranodal involvement, and the lower GI tract was the most common site of extranodal involvement (43% of the cases).

Pathologically, all cases demonstrated plasmacytic differentiation by CD38/CD138 expression. Except for one HIV-positive patient, all cases tested lacked CD20 expression. A Ki67 expression > 80% was found in eleven (52%) of the 21 patients. EBER expression was detected in 5 of the 7 (71%) HIV-positive patients tested, as opposed to 1 of 6

Table 1

Selected clinical characteristics of patients with plasmablastic lymphoma treated with bortezomib alone or in combination.

	Frontline (n = 11)	Relapsed (n = 10)
Clinical features		
Median age (range)	42 (34–80)	49.5 (19–66)
Male sex	10 (91%)	9 (90%)
IPI score > 2	6 (60%)	4 (44%)
Lugano stage III/IV	7 (70%)	9 (90%)
Extranodal involvement	11 (100%)	10 (100%)
Lower GI tract	5 (45%)	4 (40%)
Head/neck	3 (27%)	2 (20%)
Lung/pleura	3 (27%)	1 (10%)
Bone marrow	3 (27%)	2 (20%)
Skeletal bone	2 (18%)	3 (30%)
Other	4 (36%) ^a	3 (30%) ^b
HIV-positive status	6 (55%)	5 (50%)
On HAART	6 (100%)	2 (40%)

IPI: International Prognostic Index; GI: gastrointestinal; HAART: highly active anti-retroviral therapy.

^aOther sites include central nervous system (n = 1), testicle (n = 1), liver (n = 1), skin (n = 1)

^bOther sites include skin (n = 1), spleen (n = 1), muscle (n = 1)

Table 2

Selected pathological characteristics of patients with plasmablastic lymphoma treated with bortezomib alone or in combination.

Pathological features	Frontline (n = 11)	Relapsed (n = 10)
CD20	0/11 (0%)	1/10 (10%)
CD38/CD138	11/11 (100%)	10/10 (100%)
Ki67 expression > 80%	7/11 (78%)	4/5 (80%)
MYC rearrangement	6/7 (86%)	NR
EBER positive	6/9 (67%)	0/4 (0%)
HHV-8 LANA	0/6 (0%)	0/3 (0%)
ALK1	0/4 (0%)	0/1 (0%)

EBER: EBV-encoded RNA; LANA: latent nuclear antigen; ALK1: anaplastic lymphoma kinase 1.

(16%) HIV-negative patients tested. HHV8 LANA and ALK1 expression was not identified in any of the tested cases. Selected pathological characteristics are shown in Table 2.

3.2. Treatment and outcomes

In the frontline setting, the overall response rate (ORR) to bortezomib-based regimens was 100%, with complete response (CR) seen in 89% of patients. The response to bortezomib alone in the frontline setting was also 100% but all cases achieved a partial response (PR). In the relapsed setting, the ORR to bortezomib-based regimens was also 100% but the CR rate was 16%. In relapsed patients, the ORR to bortezomib alone was 75% but no CR was seen, and one patient (25%) had progressive disease. Response results are shown in Table 3. With a median follow-up time of 22 months, the median OS time of PBL patients treated with bortezomib-based regimens upfront was not reached. The 2-year OS rate was 55% (95% CI 23–78%; Fig. 1A). The OS of patients who received bortezomib alone upfront was shorter than patients who received bortezomib in combination (Fig. 2B). Of the five deaths, 3 were due to infections (2 sepsis and 1 progressive multifocal leukoencephalopathy) without evidence disease, and 2 were due to PBL relapse and progression. After a median follow-up time of 24 months, the median OS of PBL patients who received bortezomib-based regimens in the relapsed setting was 14 months with a 2-year OS rate of 27% (Fig. 2A). There was no apparent difference in OS between receiving bortezomib alone or in combination (Fig. 2B). The cause of death in all patients with relapsed PBL was progressive disease.

3.3. Analysis per HIV status

Out of the 21 patients with PBL, eleven (52%) had HIV infection. All patients in the bortezomib frontline group were on highly active anti-retroviral therapy. Of the 11 HIV-positive patients, 5 patients (45%) had a complete response (CR), 5 (45%) had a partial response and 1

Table 3

Response of plasmablastic lymphoma patients to bortezomib alone or in combination.

^aTHP-COP-bortezomib (n = 1), bortezomib-ESHAP (n = 1), bortezomib-ICE (n = 1), bendamustine-bortezomib (n = 1), bortezomib-rituximab (n = 1), VDT-PACE (n = 1).

Treatment	Frontline (n = 11)	Relapsed (n = 10)
Bortezomib-chemo	9 (82%) ^a	6 (60%) ^b
Complete response	8 (89%)	1 (16%)
Partial response	1 (11%)	5 (84%)
Bortezomib alone	2 (18%)	4 (40%)
Complete response	0 (0%)	0 (0%)
Partial response	2 (100%)	3 (75%)
Progressive disease	0 (0%)	1 (25%)

^aBortezomib-EPOCH (n = 4), bortezomib-CHOP (n = 3), R-CYBORD (n = 1), PAD (n = 1).

^bTHP-COP-bortezomib (n = 1), bortezomib-ESHAP (n = 1), bortezomib-ICE (n = 1), bendamustine-bortezomib (n = 1), bortezomib-rituximab (n = 1), VDT-PACE (n = 1).

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