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Plasmablastic Lymphoma is Treatable in the HAART Era. A 10 year Retrospective by the AIDS Malignancy Consortium (AMC)

Ariela Noy^a, Shelly Y. Lensing^b, Page C. Moore^b, Neel Gupta^c, David Aboulafia^d, Richard Ambinder^e, Robert Baiocchi^f, Bruce J Dezube^g, David Henry^h, Lawrence Kaplanⁱ, Alexandra M. Levine^j, Ronald Mitsuyasu^k, Lee Ratner^l, Erin Reid^m, Scot Remickⁿ, Joseph Sparano^o, Dimitrios Tzachanis^g, William Wachsman^m, and Amy Chadburn^p

^aMemorial Sloan-Kettering Cancer Center, and Weill-Cornell Medical College New York, NY, USA

^bUniversity of Arkansas for Medical Sciences, Little Rock, AR, USA

^cMemorial Sloan-Kettering Cancer Center, and Weill-Cornell Medical College New York, NY, USA

^dVirginia Mason Medical Center, Seattle, WA, USA

^eJohns Hopkins University (Sidney Kimmel Comprehensive Cancer Center), Baltimore, MD, USA

^fOhio State University, Columbus, OH, USA

^gBeth Israel Deaconess Medical Center, Boston, MA, USA

^hPennsylvania Oncology, Philadelphia, PA, USA

ⁱUniversity of California San Francisco, San Francisco, CA, USA

^jUniversity of Southern California, Los Angeles, CA, USA

^kUniversity of California Los Angeles, Los Angeles, CA, USA

^lWashington University in St. Louis, St. Louis, IL, USA

^mUniversity of California San Diego (UCSD Moores Cancer Center) San Diego, CA, USA

ⁿWest Virginia University, Morgantown, WV, USA

^oMontefiore-Albert Einstein Comprehensive Cancer Center, New York, NY, USA

^pNorthwestern University-Feinberg School of Medicine, Chicago, IL, USA

Plasmablastic lymphoma (PBL) is an aggressive CD20 negative diffuse large B cell lymphoma over-represented in patients with HIV infection. CD45 expression is weak, but immunoglobulin genes are rearranged and plasma cell markers are expressed.[1] In 1997, 95% of the cases were reported to be from HIV + patients, all with oral cavity involvement, 68% stage I. In this pre-HAART era report, 9/11 patients with follow-up died within a year of diagnosis. Most other case reports and case series have typically described poor survival

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for patients with PBL, particularly those infected with HIV,[2] while others were more optimistic.[³]

We sought to characterize patients with PBL diagnosed and treated solely in the HAART era. We identified 12 patients with newly diagnosed PBL treated at the AIDS Malignancy Consortium (AMC) sites from 1999 to 2008. This retrospective analysis suggests these patients had better outcomes than those identified pre-HAART, perhaps due to use of aggressive chemotherapy made possible because of better supportive care and antiretroviral therapy.

All AMC sites, which participated in this retrospective review were queried for cases of PBL diagnosed from 1998–2008. Two of the authors (AC and AN) reviewed the pathology reports for the criteria for plasmablastic lymphoma described in the 2008 WHO Classification.[4]

Twelve cases from 9 AMC sites were included in this study.

Descriptive statistics were computed for demographic and clinical characteristics. Overall survival (OS) was calculated from date of initial diagnosis to death or last follow-up. Kaplan-Meier estimates of 1-year survival were computed.

All AMC sites had an Institutional Review Board waiver of authorization.

Baseline clinical characteristics at study entry are presented in Table 1. The median CD4 + count at HIV diagnosis was 256 cells/uL (range 45–750) and was lower at initial PBL diagnosis with a median of 136 cells/uL (range of 2–514). Sixty-seven percent of the patients had had a prior opportunistic infection. Most (58%) of patients were not on HAART at lymphoma diagnosis, however, they had all previously taken HAART at some point. Of 7 patients not on HAART, 6 started HAART, typically at diagnosis or chemoimmunotherapy initiation. Stage at initial diagnosis was I (25%), II (25%), III (0%) and IV (50%). Four of 7 patients with extranodal disease had more than one site of involvement. Extranodal sites of disease at initial diagnosis included bone without bone marrow (4), bone marrow (1), liver (2), kidney (2), sinus (1), cerebrospinal fluid (1), colon (1), skin (1), adrenal (1), nasopharynx (1) and stomach (1).

Surprisingly, no patients had oral involvement. LDH was elevated in 5/8 where the value was known. The International Prognostic Index could not be calculated for the group as a whole as performance status assessment data was not available in one third of the patients. Not all cases had uniform immunophenotypic data available [Table 1]. As per the definition of plasmablastic lymphoma, all 12 cases tested were negative for the B cell marker CD20. Similarly, markers of terminal B cell differentiation, CD138 and MUM-1/IFR4, were positive in 6/6 cases and in 4/4 cases tested, respectively Epstein-Barr virus (EBV) was present in 8/8 cases based on in situ hybridization (EBER).

At initial diagnosis, 10/12 patients received chemotherapy, although HAART alone was attempted without success in one patient. Treatment was CHOP on a 14 day cycle ($n=1$) [⁵] or 21 day cycle ($n=3$), [6] (cyclophosphamide, doxorubicin, vincristine, prednisone),

infusional CDE ($n=1$), (cyclophosphamide, doxorubicin, etoposide); [7] infusional EPOCH ($n=2$) (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone), [8,9] or other ($n=5$). The other therapies included EPOCH with high dose methotrexate and zidovudine, either alternating ($n=2$), or sequential ($n=2$). Three patients with stage I/II disease received radiation in combination with chemotherapy.

Two of the ten treated patients experienced grade 3/4 toxicity. No patient died of treatment. One patient experienced grade 3/4 fatigue, anemia, thrombocytopenia, febrile neutropenia, nausea, vomiting, diarrhea, and weight loss, and the other patient experienced renal insufficiency.

Responses were complete (CR) in 7, partial (PR) in 2 and refractory in 1. CRs were seen with CHOP ($n=4$), EPOCH ($n=2$), and EPOCH alternating with high dose methotrexate and zidovudine ($n=1$). PRs were seen after EPOCH alternating with high dose methotrexate and zidovudine ($n=2$). The one patient treated with CDE had refractory disease.

Overall survival is shown in Fig. 1. At a median follow up of 73 weeks (range, 40–165), the median survival was not reached. The one-year survival was 66.7% (SE, 13.6). No patients died in the follow up period after year one.

We report the first case series of plasmablastic lymphoma patients, under the care of dedicated HIV malignancy oncologists in a consortium setting, diagnosed and treated exclusively in the HAART era. In this study we demonstrate relatively long disease free survival despite earlier reports showing nearly all HIV + patients with PBL were destined to die from progressive lymphoma.

In the initial, pre-HAART study of PBL by Delecluse, et al.^[1] 9 of the 11 patients died within 16 months of diagnosis including 3 patients with stage I disease treated with external beam radiation, poly-chemotherapy or a combination of both.

In the HAART era, intensive treatment of aggressive lymphomas, such as Burkitt and diffuse large B cell lymphoma, can result in CR and long-term survival for HIV infected patients.^[9–11] Cohort studies suggest that plasmablastic lymphoma has an inferior survival to Burkitt and DLBCL.^[12] We demonstrate that PBL may be curable, even in patients with higher stage disease and more extranodal involvement compared to the cases described by Delecluse, et al. where the disease was primarily localized to the jaw in the majority of patients.

Recently, Ibrahim et al. reported in abstract form, their single institution experience with 25 patients during the HAART era.^[13] Similar to our study, only 32% were on HAART and the median CD4 + cell count was 87cells/uL. Only 76% received chemotherapy, with EPOCH being the most common treatment choice (56%), and 28% received radiotherapy. The response rate was 84% and the median OS observed in all patients who received chemotherapy was 11.6 months (range, 2–63 months). Those who were treated with EPOCH demonstrated a better median overall survival (17 months) compared to those treated with CHOP and CHOP-like regimens (7 months, $p=0.04$).

Castillo et al. reviewed 112 cases in the literature and noted a median overall survival of 15 months with a 3 year OS of only 25%. In contrast, Cattaneo et al. reported their single institution experience of 13 patients treated during the HAART era with a 67% 3 year OS. [14] 15 patients were treated, all with CHOP or CHOP-like regimens, with involved field consolidation in seven. Five received high dose therapy with autologous stem cell transplant as first CR consolidation.

The initial goal of this AMC retrospective study was to identify which first line therapy might be the most promising for HIV positive patients with plasmablastic lymphoma. The rarity of this lymphoma resulted in a very small cohort, possibly as a result of incomplete retrieval from institutional databases. In this regard, we were unable to draw specific conclusions due to the sample size, the disparate number of lymphoma regimens, and the retrospective nature of the study. However, it is notable that CR was achieved with CHOP or EPOCH based regimens.

The literature on regimens more intensive than CHOP is inconsistent. Two earlier retrospective studies did not demonstrate an advantage of therapies more intensive than CHOP for PBL.[15,16] Loghavi et al. noted a series of 50 patients (20 HIV+) tended to have a better OS with CHOP than hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) ($p=0.078$).[17] Nonetheless, many experts do consider CHOP inadequate and favor intensive therapies including EPOCH.[18] As an aside, we cannot comment on the efficacy of HAART therapy alone, as only one patient was treated with this strategy with disease progression.

In addition to intensive chemotherapy, it is probable that our patients fared better than those in the pre- HAART era due in part to better supportive care and more robust immune status. However, we cannot be certain, as the median CD4 + cell count of 256 cells/uL at initial PBL diagnosis was relatively low. Moreover, 59% had had a prior opportunistic infection and only 29% were on HAART at PBL diagnosis.

Currently Clinical Trials Support Unit (CTSU) 9177 is prospectively studying EPOCH therapy for patients diagnosed with PBL irrespective of HIV status. Given the biologic similarity to multiple myeloma, drug classes like immune modulatory agents (IMiDs) and protease inhibitors [19] might also be promising agents for future study. The nearly ubiquitous finding of Epstein Barr in tumor tissue (11 of 12 evaluable cases in our study) may provide a rationale for viral-based strategies. Finally, the role for autologous stem cell transplant in the setting of relapsed/refractory disease is also worthy of exploration.

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References

1. Delecluse HJ, Anagnostopoulos I, Dallenbach F, et al. Plasmablastic lymphomas of the oral cavity: a new entity associated with the human immunodeficiency virus infection. *Blood*. 1997; 89:1413–1420. [PubMed: 9028965]

2. Castillo J, Pantanowitz L, Dezube B. HIV-associated plasmablastic lymphoma: lessons learned from 112 published cases. *Am J Hematol*. 2008; 83:804–809. [PubMed: 18756521]
3. Teruya-Feldstein J, Chiao E, Filippa D, et al. CD20-negative large-cell lymphoma with plasmablastic features: a clinically heterogenous spectrum in both HIVpositive and -negative patients. *Ann Oncol*. 2004; 15:1673–1679. [PubMed: 15520070]
4. Stein, H.; Harris, NL.; Campo, E. Plasmablastic lymphoma. In: Swerdlow, SH.; Campo, E.; Harris, NL., et al., editors. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue*. 4. International Agency for Research on Cancer; Lyon: France: 2008. p. 256-257.
5. Pfreundschuh M, Trumper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. *Blood*. 2004; 104:626–633. [PubMed: 14982884]
6. Fisher R, Gaynor E, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med*. 1993; 328:1002–1006. [PubMed: 7680764]
7. Sparano J, Lee S, Chen M, et al. Phase II Trial of Infusional Cyclophosphamide, Doxorubicin, and Etoposide in Patients With HIV-Associated Non-Hodgkin's Lymphoma: An Eastern Cooperative Oncology Group Trial (E1494). *J Clin Oncol*. 2004; 22:1491–1500. [PubMed: 15084622]
8. Little, R.; Pearson, D.; Franchin, G. Dose adjusted EPOCH chemotherapy in previously untreated HIV-associated non-Hodgkin's lymphoma: Preliminary report of efficacy, immune reconstitution, and HIV control following therapy. 3rd National AIDS Malignancy Conference; 1999; Bethesda (MD).
9. Little R, Pittaluga S, Grant N, et al. Highly effective treatment of acquired immunodeficiency syndromerelated lymphoma with dose-adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology. *Blood*. 2003; 101:4653–4659. [PubMed: 12609827]
10. Sparano J, Lee J, Kaplan L, et al. Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma. *Blood*. 2010; 115:3008–3016. [PubMed: 20023215]
11. Noy A, Lee J, Cesarman E, et al. AMC 048: modified CODOX-M/IVAC-rituximab is safe and effective for HIV-associated Burkitt lymphoma. *Blood*. 2015; 126:160–166. [PubMed: 25957391]
12. Schommers P, Hentrich M, Hoffmann C, et al. Survival of AIDS-related diffuse large B-cell lymphoma, Burkitt lymphoma, and plasmablastic lymphoma in the German HIV Lymphoma Cohort. *Br J Haematol*. 2015; 168:806–810. [PubMed: 25403997]
13. Ibrahim IF, SG, Naina H. Treatment of HIV-associated plasmablastic lymphoma: a single-center experience with 25 patients. *J Clin Oncol (Suppl)*. 2014; 32:8583.
14. Cattaneo C, Re A, Ungari M, et al. Plasmablastic lymphoma among human immunodeficiency virus-positive patients: results of a single center's experience. *Leuk Lymphoma*. 2015; 56:267–269. [PubMed: 24712980]
15. Castillo J, Furman M, Beltran B, et al. Human immunodeficiency virus-associated plasmablastic lymphoma: poor prognosis in the era of highly active antiretroviral therapy. *Cancer*. 2012; 118:5270–5277. [PubMed: 22510767]
16. Castillo J, Winer E, Stachurski D, et al. Prognostic factors in chemotherapy-treated patients with HIV-associated Plasmablastic lymphoma. *Oncologist*. 2010; 15:293–299. [PubMed: 20167839]
17. Loghavi S, Alayed K, Aladily T, et al. Stage, age, and EBV status impact outcomes of plasmablastic lymphoma patients: a clinicopathologic analysis of 61 patients. *J Hematol Oncol*. 2015; 8:65. [PubMed: 26055271]
18. Castillo J, Bibas M, Miranda R. The biology and treatment of plasmablastic lymphoma. *Blood*. 2015; 125:2323–2330. [PubMed: 25636338]
19. Bibas M, Grisetti S, Alba L, et al. Patient with HIVassociated plasmablastic lymphoma responding to bortezomib alone and in combination with dexamethasone, gemcitabine, oxaliplatin, cytarabine, and pegfilgrastim chemotherapy and lenalidomide alone. *J Clin Oncol*. 2010; 28:e704–e708. [PubMed: 20823416]

Figure 1.
Survival of plasmablastic lymphoma patients.

Table 1

Clinical characteristics at study entry of 12 HIV-positive patients with initial diagnosis of plasmablastic lymphoma.

Age at initial diagnosis (years), median (range)	44(18–60)	
>1 extra nodal site [number (%)]	4 (33)	
Stage at initial diagnosis, <i>n</i> (%)		
I	3 (25)	
II	3 (25)	
III	0 (0)	
IV	6 (50)	
Serum LDH (mU/mL), <i>n</i> (%)		
>Normal	5 (42)	
Normal	3 (25)	
Unknown	4 (33)	
CD4 at initial HIV diagnosis, median (range)	256 (range 45–750)	
CD4 at initial lymphoma diagnosis, median (range)	136 (2–514)	
HAART status, <i>n</i> (%)		
On	4 (33)	
Off	7 (58)	
Unknown	1 (8)	
Prior opportunistic infection, <i>n</i> (%)	8 (67)	
Immunohistochemistry	+	–
CD20	0	12
CD138	6	0
VS38c	1	0
MUM1	4	0
Ki-67 (mib-1), median (range)	95% (90–100%)	
	<i>n</i> =5	
EBER	8	0
CD45	4	2
CD15	0	2
CD30	1	4
CD79a	0	2

HIV: Human immunodeficiency virus; LDH: lactate dehydrogenase; EBER: Epstein-Barr encoding region (EBER) in situ hybridization.