Original Study

# Doxorubicin-Based Chemotherapy and Radiation Therapy Produces Favorable Outcomes in Limited-Stage Plasmablastic Lymphoma: A Single-Institution Review

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## Abstract

**Plasmablastic lymphoma is a rare, aggressive subtype of non-Hodgkin lymphoma initially described in patients infected with human immunodeficiency virus (HIV) but recently recognized in HIV-negative individuals as well. Disease most often presents as advanced, with a median overall survival time of 14 months. We examined outcomes of patients with stage I/II disease, most of whom received combined-modality therapy. Treatment was well tolerated, and long-term survival was achieved.**

**Background:** Plasmablastic lymphoma (PBL) is an aggressive variant of diffuse large B-cell lymphoma. We sought to assess the treatment outcomes after combined-modality therapy for early-stage PBL. **Materials and Methods:** We retrospectively reviewed the outcomes of 10 consecutive patients diagnosed with stage I-II PBL from February 2001 to December 2013 at a single institution. The baseline clinical characteristics, treatment modalities, overall outcomes, and treatment-related toxicity were assessed. **Results:** The median age at diagnosis was 50.5 years. All patients had extranodal disease; 2 were positive for human immunodeficiency virus. Seven patients received hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone)-based chemotherapy, 2 received CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), and 1 received dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin). Radiotherapy (RT) was administered after a complete response to chemotherapy in 7 patients and a partial response in 1 patient. At a median follow-up period of 42 months, the estimated 2-year progression-free and overall survival rates were 90% and 100%, respectively. **Conclusion:** PBL can be successfully treated with aggressive chemotherapy followed by RT. The treatment was well tolerated and can result in long-term survival for patients with limited-stage disease.

*Clinical Lymphoma, Myeloma & Leukemia,* Vol. 16, No. 3, 122-8 
**Keywords:** Combined modality therapy, Early stage, Non-Hodgkin lymphoma, Radiotherapy, Survival

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Submitted: Sep 3, 2015; Revised: Nov 27, 2015; Accepted: Dec 15, 2015; Epub: Dec 22, 2015

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2152-2650/$ - see frontmatter 
http://dx.doi.org/10.1016/j.clml.2015.12.008

## Introduction

Plasmablastic lymphoma (PBL) is an aggressive type of non-Hodgkin lymphoma (NHL) that was initially described in the late 1990s as a new clinical entity in patients with human immunodeficiency virus (HIV) infection. In the original case description, 16 patients, of whom 15 were HIV-positive, presented with oral cavity involvement and an aggressive clinical course with poor outcomes.[1] Currently, PBL is recognized by the World Health Organization as an aggressive type of NHL that is more often seen in patients with HIV infection or other types of immunodeficiency, although about 30% of cases occur in apparently immunocompetent patients.[2-4]

Pathologically, PBL is characterized by large lymphoma cells that often resemble B immunoblasts but have a plasmacytic immunophenotype, with loss of pan B-cell markers such as CD20, PAX-5, and CD79a, and expression of plasma cell-associated markers such as CD38 and CD138 and MUM1/IFR4.[4] Genetic profiling analysis has shown that the genetic signature of PBL cells is more closely aligned with that of diffuse large B cell lymphoma.[5] These tumors have a nongerminal center B-cell immunophenotype.[4] An association with Epstein-Barr virus (EBV) has been documented,[2] and *MYC* gene arrangements have been reported in up to one half of cases.[6,7]

Roughly 60% of patients with PBL present with advanced, Ann Arbor stage III or IV disease.[2] Oral cavity involvement is typical; however, intraoral involvement was found in 1 review to be more common in HIV-positive patients than in HIV-negative patients (58% vs. 16%).[2] Nodal, cutaneous, and gastrointestinal sites are also affected.[8] The initial therapy has most often been cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens. Rituximab, an anti-CD20–targeted antibody, is usually not used because PBL does not express CD20. However, the outcomes from this approach have been disappointing, with a median overall survival (OS) of only about 14 months and 5-year OS rate of 31%.[8] The National Comprehensive Cancer Network guidelines have advocated the use of more intensive initial therapy, such as dose-adjusted etoposide, prednisone, vincristine, doxorubicin, and cyclophosphamide (DA-EPOCH) or fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD). However, the results have been mixed regarding an improvement in outcomes.[9-12]

A role for consolidative radiation therapy (RT) in the treatment of patients with diffuse large B cell lymphoma has recently become apparent, with findings emerging that highlight improvements in event-free survival and potentially OS in patients who receive consolidative RT.[9-11] In the ongoing UNFOLDER trial (Unfavorable Low-Risk Patients Treated with Densification of R-Chemo Regimens; ClinicalTrials.gov identifier, NCT00278408), a 2 × 2 randomized trial comparing R-CHOP on a 14- or 21-day schedule with or without consolidative RT for patients with stage I-IV diffuse large B cell lymphoma, the no-RT groups were closed early when a statistically significant difference in event-free survival was observed on interim analysis. To date, however, no series has evaluated the effect of RT for PBL, probably because of the rarity of the disease and its predilection for presenting at advanced stages, when RT is perceived to have little role. In the present analysis, we evaluated the outcomes of patients with limited-stage PBL treated at our institution with and without RT in an attempt to clarify whether RT is useful in this situation.

## Materials and Methods

The appropriate institutional review board approved the present retrospective analysis. We identified 11 consecutive patients with limited-stage (stage I or II) PBL treated at our institution from February 2001 through December 2013. Of these 11 patients, 10 completed therapy at our center and were included in the present report.

Disease was staged according to the Ann Arbor staging system. The full workup consisted of core or excisional biopsy; baseline $^{18}$F-fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT) or, for 1 patient treated before routine use of PET-CT, gallium scanning; baseline contrast-enhanced CT; basic laboratory studies; HIV testing; serum and urine protein electrophoresis; and bilateral bone marrow biopsy.

### *Chemotherapy*

Hyper-CVAD consisted of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with methotrexate and cytarabine.[12] CHOP chemotherapy involved cyclophosphamide, vincristine, doxorubicin, and prednisone.[13] DA-EPOCH consisted of dose-adjusted etoposide, doxorubicin, and cyclophosphamide administered with vincristine and prednisone.[14,15]

### *Radiation Therapy*

External beam RT was given as consolidation, with involved field or involved site targeting.[16,17] Involved site RT was administered with the goal of treating prechemotherapy sites of disease involvement with a margin, according to the guidelines from the International Lymphoma Radiation Oncology Group.[17] Intensity-modulated RT (IMRT) or volumetric modulated arc therapy (VMAT) was often used to spare the normal tissues in the head and neck, the salivary glands in particular.

### *PET-CT Evaluation of Response*

Two experts in the interpretation of PET-CT scans (1 nuclear medicine physician and 1 radiologist) retrospectively and independently reviewed all the PET-CT scans. One patient had undergone PET-only imaging (and did not receive RT); all other patients had undergone PET-CT imaging. PET-CT has been used throughout to refer to either PET only or PET-CT. On completion of therapy, the response was assessed according to the International Working Group criteria for PET-CT for end-of-treatment evaluation.[18] A 5-point scoring system (5-PS; also known as the Deauville criteria) was used to assess the response. In the 5-PS, based on the avidity of the mediastinal and liver blood pools, 1 denotes no uptake over background; 2, uptake less than that of the mediastinal blood pool; 3, uptake greater than that of the mediastinal blood pool but less than that of the liver; and 4 and 5, moderately or markedly greater than liver uptake, respectively. Scores of 1 to 3 are consistent with a complete response, regardless of whether a residual mass is present. A partial response is indicated by a score of 4 or 5, with reduced uptake compared with the baseline scan. Stable disease is defined as a score of 4 or 5 with no significant change in avidity. Progressive disease is defined as scores of 4 to 5 with increased uptake relative to the baseline study or evidence of new avid foci of involvement.