

# ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

## Advances in the Management of Primary Central Nervous System Lymphoma



**Kieron Dunleavy, MD**  
 Professor of Medicine  
 George Washington University  
 Director of Lymphoma  
 GW Cancer Center  
 Washington, DC

### H&O What is primary CNS lymphoma?

**KD** Primary central nervous system (CNS) lymphoma is a subtype of diffuse large B-cell lymphoma (DLBCL), the most common type of non-Hodgkin lymphoma (NHL). Approximately 3% to 4% of cases of DLBCL are primary CNS lymphoma. This lymphoma is unique because it starts in the CNS, and, in most cases, is confined there. It does not usually spread systemically. Most patients are aged 60 years or older.

Although it is a subtype of DLBCL, primary CNS lymphoma is distinct not only in the part of the body that it affects but also in its pathology and molecular

Treatments for CNS lymphoma must cross the blood-brain barrier, and therefore they differ from those that are standard for DLBCL.

biology. Most systemic DLBCL cases can be divided into 1 of 2 molecular subtypes based on cell of origin: germinal center B-cell (GCB) subtype and activated B-cell (ABC) subtype. The molecular biology of primary CNS

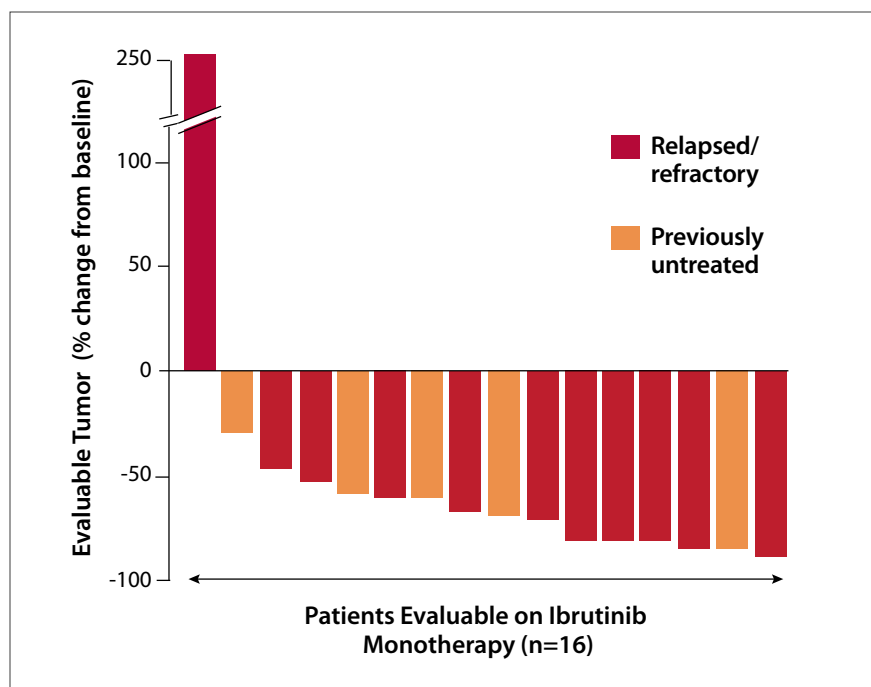
lymphoma closely resembles that of the ABC subtype, but it is not identical. Its mutational profile differs, and most patients with primary CNS lymphoma have mutations in the B-cell receptor signaling pathway and/or the toll-like receptor signaling pathway.

### H&O How is primary CNS staged and/or monitored?

**KD** There is a distinct staging workup agreed upon by an international primary CNS group. Patients with primary CNS lymphoma undergo magnetic resonance imaging of the brain, and their spinal fluid is checked at diagnosis by both cytology and flow cytometry. As with all lymphomas, a biopsy reviewed by a hematopathologist who is an expert in diagnosing lymphomas is essential at diagnosis.

### H&O What are the standard treatments for primary CNS lymphoma?

**KD** Treatments for CNS lymphoma must cross the blood-brain barrier, and therefore they differ from those that are standard for DLBCL. In the past, most patients received methotrexate-based therapy, sometimes with cytarabine and also rituximab (Rituxan, Genentech/Biogen), which is standard in B-cell lymphomas. Owing to poor outcomes with standard approaches, whole brain radiation treatment has been used frequently in this disease. The treatment landscape is currently shifting, and new agents such as Bruton tyrosine kinase (BTK) inhibitors, immunomodulatory drugs, and immune checkpoint inhibitors



**Figure.** In a recent study, ibrutinib monotherapy in primary central nervous system lymphoma showed very high efficacy. Reprinted from *Cancer Cell*, Volume 31, Issue 6. Lionakis MS et al. Inhibition of B cell receptor signaling by ibrutinib in primary CNS lymphoma. Pages 833-843. Copyright 2017, with permission from Elsevier.

have recently demonstrated good activity. With standard approaches, approximately 25% of patients with primary CNS lymphoma are alive 5 years after initial diagnosis and—unlike the case with systemic DLBCL—there are a high number of late relapses.

### **H&O** How are new insights into the biology and microenvironment of primary CNS lymphoma informing treatment?

**KD** As I mentioned, the molecular biology of primary CNS lymphoma resembles the ABC subtype of DLBCL. A high proportion of patients have a CD79B mutation in the B-cell receptor and/or a MYD88 mutation. In a study of patients with systemic DLBCL, the Bruton tyrosine kinase inhibitor ibrutinib (Imbruvica, Pharmacyclics/Janssen) was preferentially active in the ABC subtype, with a response rate of approximately 40%. This finding prompted the evaluation of ibrutinib in primary CNS lymphoma, and recent studies have shown high response rates. However, most patients develop relapsed or progressive disease within 6 to 8 months.

The roles of the microenvironment and host-tumor cell interactions appear to be important in primary CNS lymphoma. Studies are evaluating the immune checkpoint inhibitors nivolumab (Opdivo, Bristol-Myers Squibb) and pembrolizumab (Keytruda, Merck) in primary CNS lymphoma. Some very early data suggest that this approach is promising.

Many other therapies have been developed or tested

based on our understanding of the tumor biology of this disease. Studies of immunomodulatory drugs (IMiDS), such as lenalidomide (Revlimid, Celgene), have shown efficacy in this setting.

### **H&O** Are there particular challenges for these patients in terms of clinical trial design and treatment?

**KD** There are several challenges when designing trials for patients with primary CNS lymphoma. This population of patients frequently has a poor performance status at diagnosis, which makes instituting clinical trials challenging. Also, because primary CNS lymphoma is rare, it can be challenging to find patients for clinical trials. There has been a high level of dependence on therapies that cross the blood-brain barrier, such as methotrexate, cytarabine, and whole brain radiation.

At the National Cancer Institute, we recently published a study evaluating a regimen called DA-TEDDI-R in patients with primary CNS lymphoma, most of whom had relapsed or refractory disease. The DA-TEDDI-R regimen is based on a standard regimen used for systemic DLBCL, with substitutions for drugs that do not cross the blood-brain barrier. The regimen consists of temozolomide (Temodar, Merck), etoposide, doxorubicin, dexamethasone, ibrutinib, and rituximab, with intraventricular cytarabine. As part of the study, patients received 14 days of ibrutinib before treatment with DA-TEDDI-R. There was very high efficacy with

ibrutinib alone, and this outcome has also been shown by 2 other groups (Figure). More than 80% of patients had a good response to ibrutinib alone, and DA-TEDDI-R was effective in many patients with relapsed or refractory disease.

### H&O Do genetic mutations correspond to treatment outcomes?

**KD** We attempted to evaluate this in our study, but the limited number of cases precludes any definitive conclusions. In a trial of ibrutinib in systemic DLBCL, certain genetic mutations were associated with different clinical outcomes, but the number of cases was limited.

### H&O Are there any other novel approaches that appear promising?

**KD** A regimen consisting of methotrexate, cytarabine, thiotepa, and rituximab (MATRix) was associated with a very good outcome in a European trial of patients with newly diagnosed primary CNS lymphoma. At a median follow-up of 30 months, the complete remission rate was 49% among patients treated with the MATRix regimen, compared with 23% in those treated with methotrexate/cytarabine alone and 30% of those treated with methotrexate/cytarabine plus rituximab.

In the United States, the role of autologous transplant is being tested in a phase 2 trial from the Alliance for Clinical Trials in Oncology. After induction therapy, patients will be randomly assigned to receive treatment with stem cell transplant or consolidation chemotherapy. High-dose therapy has now been tested in several studies, but it is not clear if it is helpful when patients have a good response to initial therapy.

As already mentioned, strategies that inhibit the B-cell receptor signaling pathway and/or toll-like receptor signaling pathway are interesting, as are immune checkpoint inhibitors and agents such as lenalidomide. Chimeric antigen receptor (CAR) T-cell therapy is another interesting approach to consider, although this strategy has not yet been tested in primary CNS lymphoma. Several trials are currently evaluating CAR T-cell therapies in DLBCL, and primary CNS lymphoma may be a subtype

of DLBCL that could be particularly responsive to this type of strategy.

### H&O What is the role of maintenance therapy?

**KD** Although maintenance therapy is used in indolent lymphomas, there is no proven role in DLBCL. With the advent of newer agents, however, the role of maintenance therapy will be evaluated in future clinical trials.

#### Disclosure

*Dr Dunleavy has no real or apparent conflicts of interest to report.*

### Suggested Readings

Chen YB, Batchelor T, Li S, et al. Phase 2 trial of high-dose rituximab with high-dose cytarabine mobilization therapy and high-dose thiotepa, busulfan, and cyclophosphamide autologous stem cell transplantation in patients with central nervous system involvement by non-Hodgkin lymphoma. *Cancer*. 2015;121(2):226-233.

ClinicalTrials.gov. Combination chemotherapy with or without autologous stem cell transplant in treating patients with central nervous system B-cell lymphoma. <https://clinicaltrials.gov/ct2/show/NCT01511562>. Identifier: NCT01511562. Accessed June 19, 2017.

ClinicalTrials.gov. A study of nivolumab in relapsed/refractory primary central nervous system lymphoma (PCNSL) and relapsed/refractory primary testicular lymphoma (PTL) (CheckMate 647). <https://clinicaltrials.gov/ct2/show/NCT02857426>. Identifier: NCT02857426. Accessed June 22, 2017.

Ferreri AJ, Cwynarski K, Pulczynski E, et al; International Extranodal Lymphoma Study Group (IELSG). Chemotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. *Lancet Haematol*. 2016;3(5):e217-e227.

Ghesquieres H, Houillier C, Chinot O, et al. Rituximab-lenalidomide (REVR) in relapse or refractory primary central nervous system (PCNSL) or vitreo retinal lymphoma (PVRL): results of a "proof of concept" phase II study of the French LOC Network [ASH abstract 785]. *Blood*. 2016;128(suppl 22).

Grommes C, Pastore A, Palaskas N, et al. Ibrutinib unmasks critical role of Bruton tyrosine kinase in primary CNS lymphoma [published online June 15, 2017]. *Cancer Discov*. 2017;CD-17-0613. doi:10.1158/2159-8290.

Houillier C, Choquet S, Touitou V, et al. Lenalidomide monotherapy as salvage treatment for recurrent primary CNS lymphoma. *Neurology*. 2015;84(3):325-326.

Lionakis MS, Dunleavy K, Roschewski M, et al. Inhibition of B cell receptor signaling by ibrutinib in primary CNS lymphoma. *Cancer Cell*. 2017;31(6):833-843.e5.

Nayak L, Iwamoto FM, LaCasce A, et al. PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma. *Blood*. 2017;129(23):3071-3073.

Wilson WH, Young RM, Schmitz R, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. *Nat Med*. 2015;21(8):922-926.