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 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.

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

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
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/rituximab alone and 30% of those treated with methotrexate/rituximab 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**


