Central nervous system (CNS) lymphomas in immunocompetent patients are predominantly B-cell lymphoid malignancies that have heterogeneous presentations in the brain, spinal cord, and subarachnoid space, whereas only 5% have T-cell phenotype (1). Unlike their systemic counterparts, CNS lymphomas present a formidable challenge for neuro-oncologists due to toxicities associated with conventional chemotherapies because of poor specificity and the blood-brain barrier that limits systemically given chemotherapies into the brain and subarachnoid space. Our incomplete understanding of the underlying biology also hampers efforts to design better treatments. Although high-dose methotrexate (2–6) remains the standard therapy at present, it has major limitations. This review will highlight the multifaceted nature of CNS lymphomas and the challenges and opportunities in using mAbs for CNS lymphomas.

Pleomorphic Presentations of Central Nervous System Lymphomas

Lymphomas in the CNS have pleomorphic presentations, and they could be separated into four major categories: systemic lymphomas that metastasized to the CNS, primary CNS lymphomas, primary ocular lymphomas, and CNS intravascular lymphomatosis (Table 1). It is important to point out that this classification is imprecise, because it is based on clinicopathologic behavior and not on molecular features. Unlike systemic non-Hodgkin’s lymphomas in which patients could undergo repeated lymph node biopsies with acceptable risk, brain tissues from patients with CNS lymphoma cannot be so easily obtained because of potentially serious complications associated with craniotomies. This is further complicated by rapidly progressive neurologic deterioration in patients that requires dexamethasone treatment before brain biopsy. Thus, the diagnostic B-lymphoma cells frequently disappear from biopsied tissues. Nevertheless, existing data suggest that lymphoma metastasis is the most common form of CNS lymphomas. Intermediate-grade and high-grade lymphomas have the greatest propensity of CNS spread, and their respective frequencies are 6.5% and 16.7% (7, 8). Angiocentricity of lymphoma cells (Fig. 1) is a typical histologic feature in brain parenchyma, but leptomeningeal spread is possible and often occurs simultaneously. Other noteworthy clinical features, such as lymphomatous involvement of testes, paranasal sinuses, orbits, and bone marrow, increase the risk of CNS spread (7, 8).

The second major category of lymphomas in CNS is primary CNS lymphomas. Although they are also angiocentric, primary CNS lymphomas have a propensity of invading adjacent white matters, resulting in homogeneously enhancing masses that follow the contour of white matter or corpus callosum on magnetic resonance imaging (Fig. 2). In addition to presentation as a solitary mass, primary CNS lymphomas may show up as multiple subependymal nodules or as leptomeningeal collection of lymphoma, also known as meningoencephalitic form of primary CNS lymphoma (1) and primary leptomeningeal lymphoma (9, 10), respectively. Furthermore, T cells are found in the vicinity of B-lymphoma cells (11) and may have a role in sustaining and propagating these B-lymphoma cells. Whether or not these T cells are αβ or γδ subtypes, have monoclonal or polyclonal T-cell receptor rearrangements, or...
function in a reactive mode or help to maintain the viability of B-lymphoma cells remain to be determined.

The presenting signs and symptoms of primary ocular lymphomas are nonspecific, primarily consist of floaters and blurry vision. A disproportionate number of patients are elderly over the age of 60. Unlike other diseases of the retina in this population, such as benign inflammatory uveitis and macular degeneration, the tempo of vision loss is rapid and occurs over weeks. A slit lamp examination may provide a clue to diagnosis, because clumps of floating lymphoma cells can be seen, and retina may show signs of choroidal lymphoma infiltrates or vasculopathy manifesting as leakage of fluorescein dye (12). A vitreous aspiration may be diagnostic if lymphoma cells are seen on cytologic or flow cytometry examination (13). Because the eyes are extensions of the brain from a developmental perspective, it is not surprising that these patients frequently have lymphomatous spread into the CNS. In fact, it is not unusual for primary ocular lymphomas to be diagnosed only when CNS lymphomas are detected. Therefore, this disorder should be considered in the elderly with rapid vision loss.

Primary intravascular lymphomatosis is a rare but unusual form of CNS lymphomas, as the lymphoma cells seem stuck in the lumena of cerebral vasculature (Fig. 3). Patients present with multiple and recurrent stroke-like events (14, 15), and lesions are without enhancement on magnetic resonance imaging. Although timely diagnosis by a brain biopsy and treatment may reverse neurologic deficits (16, 17), most patients are diagnosed too late in the course of their disease.

### Assumptions in Central Nervous System Lymphomas

There are a number of assumptions made about the nature of CNS lymphomas, and these assumptions may lead to the design of suboptimal therapies. Separating CNS lymphomas into the above four categories seems rather arbitrary, because they are all within a spectrum of extranodal lymphomas in the CNS. Some investigators would even argue that primary CNS lymphomas may not be exclusive to the CNS but are residual systemic lymphomas that have escaped systemic immune surveillance and purging (18). There is support for this concept, because B lymphocytes typically do not reside in the brain, except at times of infection or noninfectious inflammatory state. Furthermore, unlike primary gliomas in the brain in which analogous platelet-derived growth factor receptor and epidermal growth factor receptor signal transduction pathways are important for the development and maintenance of native glial cells, CNS lymphomas are driven by signal transducers and activators of transcription and Janus-activated kinase signaling pathways (19) that are not used by intrinsic cells in the CNS (Table 2). Immunohistochemical staining of key antigens in primary gliomas and CNS lymphomas also highlights differences between these brain tumors. Primary gliomas have positive staining for glial fibrillary acidic protein, which is also found in normal glial cells. However, CD20 antigen, which is a common antigen in normal and malignant B cells, is nowhere to be found in neurons or glia (Table 2). Third, there are striking similarities between primary CNS lymphomas and CNS intravascular lymphomatosis. In primary CNS lymphomas, the lymphoma cells are located in the brain parenchyma and

<table>
<thead>
<tr>
<th>Type</th>
<th>Histologic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic CNS lymphomas</td>
<td>Angiocentric</td>
</tr>
<tr>
<td>Primary CNS lymphomas</td>
<td>Angiocentric and invasive</td>
</tr>
<tr>
<td>Primary ocular lymphomas</td>
<td>Originated in the eye (i.e., vitreous humor, choroidal membrane, or retinal vasculature) with a propensity for CNS spread</td>
</tr>
<tr>
<td>CNS intravascular lymphomatosis lymphomas</td>
<td>Primarily aggregate in the lumena of brain vasculature</td>
</tr>
</tbody>
</table>
surround blood vessels. In CNS intravascular lymphomatosis however, the lymphoma cells seem stuck in the lumena of blood vessels on their way into the brain or subarachnoid space. This migrational defect could be a result of differences in \( \beta_1 \) and intercellular adhesion molecule-1 expression that help lymphoma cells trafficking from systemic circulation into the brain or subarachnoid space (20). Lastly, there are tantalizing molecular data to suggest a systemic origin for primary CNS lymphomas. Pels et al. (21) reported a patient with primary CNS lymphoma who had the same immunoglobulin gene rearrangement but different sets of somatic mutations in surgical specimens obtained at initial diagnosis and at disease recurrence, suggesting that there was a common clonal precursor for both lymphoma specimens.

Because CNS lymphomas are traditionally thought to be malignancies present exclusively in the CNS, drug treatment were designed to overcome pharmacokinetic obstacles posed by the blood-brain barrier. However, evidence for a common clonal progenitor for CNS lymphomas suggests that drug treatment directed primarily to the CNS may not be enough. A concerted treatment approach to both CNS and systemic sources of lymphoma may be necessary (18). Traditional cytotoxic chemotherapies also suffered from low specificity for B-lymphoma cells. The high target specificities of mAbs would offer increased efficacy for eradicating systemic lymphoma cells. Although mAbs are large molecules, they may leak across sites with disrupted blood-brain barriers and their high target specificity would still have therapeutic efficacy for lymphoma cells in the CNS (18).

**Limitations of Existing Treatment Modalities**

The principal treatment modality for CNS lymphomas is high-dose methotrexate. Although it is excluded by the blood-brain barrier due to its large molecular size and hydrophilicity, methotrexate could still penetrate the brain parenchyma when rapidly infused at high doses. Its efficacy is suboptimal because it only produces a complete response rate of 0% to 60% before cranial irradiation (2–6). Although methotrexate delivery to the CNS could be improved with osmotic blood-brain barrier disruption (22, 23), an equally important treatment issue has to do with the emergence of resistant clones of lymphoma cells. Treating CNS lymphomas with single-agent methotrexate alone or in sequential combination with other chemotherapies is in distinct contrast to combination chemotherapy regimens that are used for systemic non-Hodgkin’s lymphomas. Regimens that are used for systemic lymphomas, such as cyclo-phosphamide, doxorubicin, vincristine, and prednisone; methotrexate, cyclophosphamide, doxorubicin, vincristine, and prednisone; and etoposide, methylprednisolone,
high-dose cytarabine, and cisplatin (24, 25), were all designed based on the concept of simultaneous multiagent chemotherapies with different mechanisms of action and nonoverlapping toxicity to prevent the emergence of drug-resistant lymphoma clones. The fact that primary CNS lymphoma has an overall survival less than that for systemic lymphoma, 3-year survival 30% versus 50% (2, 24), may be a result of such single-agent treatment. Unfortunately, drugs such as cyclophosphamide, doxorubicin, and vincristine do not work for CNS lymphomas, because they are large water-soluble molecules excluded by the blood-brain barrier (26, 27). Likewise, in pediatric non-Hodgkin’s lymphomas, multiagent combination chemotherapy regimens, including cyclophosphamide, doxorubicin, etoposide, methotrexate, cytarabine, vincristine, and intrathecal methotrexate, have produced increased event-free survival across all stages of disease, including those with lymphomatous involvement in the CNS (28, 29). However, dose intensification of methotrexate and cytarabine in patients with CNS disease resulted in increased toxicity (28, 29). Furthermore, the relative efficacy and toxicity of delivering systemic chemotherapy into the brain by osmotic blood-brain barrier disruption remains to be determined (30).

In addition to the brain parenchyma, lymphoma in the subarachnoid space requires a different therapeutic strategy. Although high-dose methotrexate and high-dose cytarabine could penetrate the cerebrospinal fluid space, intrathecal injection of chemotherapy is the primary treatment modality (31) and the prolonged pharmacokinetic profile of liposomal cytarabine has proven efficacy for lymphomatous meningitis (32). However, intrathecal chemotherapy has no effect on parenchymal brain lymphomas, because penetration into the brain parenchyma is at most 3 mm from the ependymal surface (33). Craniospinal irradiation would limit further chemotherapy treatment, and palliative radiotherapy is only used to treat symptomatic sites in the neuraxis.

Another shortcoming of high-dose methotrexate has to do with its clearance. Because methotrexate is primarily cleared renally, patients must have adequate glomerular filtration. Methotrexate could be given at full doses (range, 3.5-8.0 g/m²) when patients’ creatinine clearance is ≥90 mg L/min. When the creatinine clearance decreases below 90 mg L/min, a dose reduction of methotrexate proportional to the drop in creatinine clearance would be necessary to prevent the emergence of systemic toxicities like mucositis, leukopenia, thrombocytopenia, elevated liver enzymes, and leukoencephalopathy. In addition, patients with cardiomyopathy cannot withstand aggressive fluid hydration, whereas those with diabetic nephropathy or transplanted kidney risk losing their kidneys.

Another major problem associated with high-dose methotrexate is neurotoxicity. Elderly patients are particularly susceptible to developing a subacute leukoencephalopathy, characterized by dementia, unsteady gait, and urinary incontinence, as a result of methotrexate damage to white matter of the brain (34, 35). This side effect, when severe, can be detected as hyperintense signals on T2 and FLAIR magnetic resonance imaging, and it could occur even without whole brain cranial irradiation. Although one could minimize the risk of leukoencephalopathy by administering high-dose methotrexate before or without consolidative cranial irradiation, this type of methotrexate-induced neurotoxicity is not reversible despite our best effort to prevent it.

### Table 2. Differences between primary CNS lymphomas and primary gliomas

<table>
<thead>
<tr>
<th>Normal brain</th>
<th>Primary gliomas</th>
<th>Primary CNS lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glial cells</td>
<td>Cells of glial origin</td>
<td>B cells</td>
</tr>
<tr>
<td>GFAP+</td>
<td>GFAP+</td>
<td>CD20+</td>
</tr>
<tr>
<td>PDGFR/EGFR signaling</td>
<td>PDGFR/EGFR signaling</td>
<td>STAT/JAK signaling</td>
</tr>
</tbody>
</table>

Abbreviations: PDGFR, platelet-derived growth factor receptor; EGFR, epidermal growth factor receptor; STAT, signal transducers and activators of transcription; JAK, Janus-activated kinase.
Emerging Monoclonal Antibody Treatments for Central Nervous System Lymphomas

In the past 5 years, the emergence of mAb therapies for lymphoproliferative malignancies has expanded the therapeutic option for CNS lymphomas. Although they are large molecules excluded by an intact blood-brain barrier, mAbs could leak across permeable tumor vasculature into CNS lymphomas. More importantly, the favorable pharmacodynamic properties of mAbs may overcome their pharmacokinetic limitations, as their high specificity targeting lymphoma cells does not necessitate a high concentration in CNS lymphomas, and may result in a better therapeutic index than methotrexate. Another advantage of mAbs is their lack of pharmacodynamic interactions with conventional chemotherapies and anticonvulsants. Their combination with conventional chemotherapies may result in a synergistic therapeutic response.

Immunochemotherapy with rituximab and temozolomide. Rituximab (Rituxan) is a chimeric murine mAb against the CD20 antigen on B-lymphoma cells. Its mechanisms of action include complement-mediated cytotoxicity, antibody-mediated phagocytosis, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent growth inhibition and apoptosis (36). As a single agent, it had limited efficacy against CNS lymphomas, because it only produced partial responses (37). This may be due to the poor penetration of rituximab into the cerebrospinal fluid, which is 0.1% of that in the serum (38). However, intrathecal administration of rituximab increases the level in the cerebrospinal fluid (39). Whether or not this would result in an increase in efficacy remains to be determined. Furthermore, single-agent temozolomide (Temodar), an alkylator that does not have cumulative myelotoxicity, was used to treat CNS lymphomas (40, 41). However, when the two agents were combined, rituximab, and temozolomide resulted in a 70% response rate in a group of elderly patients with poor renal functions (42). Three of the cohort (40%) had durable responses that lasted for 26, 23, and 12 months to date (33) (Table 3). Other investigators also noted a 53% objective response rate in relapsed primary CNS lymphomas (44). The toxicity of rituximab and temozolomide consisted of myelosuppression and was primarily related to the temozolomide dose. The data available thus far suggest that rituximab and temozolomide combination has efficacy against CNS lymphomas and this immunochemotherapy combination has acceptable toxicity. A prospective evaluation would be warranted.

Radioimmunotherapy with yttrium-90 (90Y) ibritumomab tiuxetan or iodine-131 (131I) tositumomab. 90Y ibritumomab tiuxetan (Zevalin) and 131I tositumomab (Bexxar) are murine mAbs against CD20 antigen that are conjugated to a radioactive label. Such as epratuzumab, epratuzumab has shown efficacy against indolent and aggressive non-Hodgkin’s lymphomas. Although its precise function in B-cell lymphomas, its high specificity targeting lymphoma cells is unclear, CD20 seems to mediate survival and migration (47, 48). As a single agent, epratuzumab offers an added efficacy against B-cell lymphomas. Although radiation in general has a neurotoxic effect in the CNS, both antibodies give off low-dose rate radiation. Compared with high-dose rate radiation from conventional external beam cranial irradiation, low-dose rate radiation may result in a synergistic therapeutic response, whereas CNS toxicity is minimized. The systemic toxicities, however, consist of asthenia and infusion reactions such as rigors, fevers, and nausea (45). Myelosuppression is a major toxicity because both antibodies also accumulate in the bone marrow, and patients with low bone marrow reserve are at risk for neutropenia, thrombocytopenia, or both (45).

Epratuzumab. Epratuzumab, a humanized mouse anti-CD22 mAb, has shown efficacy against indolent and aggressive non-Hodgkin’s lymphomas. Although its precise function in B-lymphoma cells is unclear, CD22 seems to mediate survival and migration (47, 48). As a single agent, epratuzumab offers an objective response rate of 43% for follicular lymphomas (49) and 10% for aggressive lymphomas (50). Like rituximab alone, epratuzumab as a single agent probably has limited efficacy against aggressive lymphomas in the CNS. But its efficacy may be improved with concomitant cytotoxic chemotherapies, such as dexamethasone and this immunochemotherapy combination has acceptable toxicity. A prospective evaluation would be warranted.

Table 3. Durable responses in patients treated with rituximab and temozolomide

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Disease</th>
<th>Cycles of R + T</th>
<th>Dose of T (mg/m²/d)</th>
<th>Cycles of T</th>
<th>Response</th>
<th>Duration of response (mo)</th>
<th>Survival (mo)</th>
<th>Initial CSF cytology</th>
<th>Intrathecal chemotherapy</th>
<th>Final CSF cytology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 64</td>
<td>26</td>
<td>CD20+ relapsed PCNSL</td>
<td>4</td>
<td>150</td>
<td>8</td>
<td>CR</td>
<td>23+</td>
<td>23+</td>
<td>Negative</td>
<td>None</td>
<td>Negative</td>
</tr>
<tr>
<td>2 71</td>
<td>23</td>
<td>CD20+ relapsed PCNSL</td>
<td>4</td>
<td>200</td>
<td>8</td>
<td>CR</td>
<td>12+</td>
<td>12+</td>
<td>Negative</td>
<td>None</td>
<td>Negative</td>
</tr>
<tr>
<td>3 76</td>
<td>12</td>
<td>NHL relapsed in the brain only, CD20+</td>
<td>4</td>
<td>75-150</td>
<td>8</td>
<td>CR</td>
<td>26+</td>
<td>26+</td>
<td>Negative</td>
<td>None</td>
<td>Negative</td>
</tr>
</tbody>
</table>

NOTE: All patients received 375 mg/m² of rituximab.
Abbreviations: R, rituximab; T, temozolomide; NHL, non-Hodgkin’s lymphoma; CSF, cerebrospinal fluid; CR, complete response.
as temozolomide. More importantly, the side effects of epratuzumab are mild and primarily consist of fatigue in 22% and 18% of treated patients (49, 50).

**Alemtuzumab.** Alemtuzumab (Campath-1H) is a humanized mAb against CD52 antigen on B- and T-lymphoma cells. In clinical trials for chronic lymphocytic leukemia, it has a response rate of 38% and a median time to tumor progression of 15.4 months (51–53). However, alemtuzumab has less efficacy against relapsed non-Hodgkin's lymphoma, with a response rate of 8% to 17% (54, 55), and this low response rate could be due to variable expression of CD52 antigen in B-lymphoma cells. Although preclinical data is lacking at present, alemtuzumab may be an option in selected patients with CD52 expression in biopsy specimens, or it may help to remove T cells that support the viability of B-lymphoma cells in the CNS. Further clinical studies would be necessary to define the therapeutic index, because alemtuzumab can cause a profound loss of T lymphocytes, resulting in cell-mediated immunosuppression and opportunistic infections such as herpes zoster reactivation or Pneumocystis pneumonia (51–53).

**Natalizumab.** Natalizumab (Antegren) is a humanized mAb against α4β7 integrin on CD4+CD25+ T-cells. Such immunotherapy, radioimmunotherapy, or immunochemo-therapy combination, like rituximab and temozolomide, 111In ibritumomab tiuxetan, 131I tositumomab, alemtuzumab, epratuzumab, and natalizumab, may offer treatments for CNS lymphomas with a better therapeutic index than existing methotrexate-based therapies.

**Conclusion**

The management of CNS lymphomas is poised for another revolution with emergence of mAbs with high specificity against lyphoma cells. Such immunotherapy, radioimmunotherapy, or immunochemo-therapy combination, like rituximab and temozolomide, 111In ibritumomab tiuxetan, 131I tositumomab, alemtuzumab, epratuzumab, and natalizumab, may offer treatments for CNS lymphomas with a better therapeutic index than existing methotrexate-based therapies.

**References**

18. Wong ET. Correspondence: immunochemotherapy for CNS lymphoma: a randomized, double-blinded, placebo-controlled trials for relapsing-remitting multiple sclerosis, natalizumab was found to decrease cerebral inflammation as detected on gadolinium-enhanced magnetic resonance imaging (56, 57). Because α4 integrin is expressed by mantle zone lymphocytes and strong immunohistochemical staining of α4 integrin correlates with poor survival in patients with diffuse large cell lymphomas (58), natalizumab may stop the trafficking of B-lymphoma cells from systemic circulation into the CNS and block the invasive behavior of primary CNS lymphomas in the brain.

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Management of Central Nervous System Lymphomas Using Monoclonal Antibodies: Challenges and Opportunities

Eric T. Wong


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