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Lymphomatous Meningitis in Primary Central Nervous System Lymphoma

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Neurosurg Focus. 2006;21(5)

Abstract and Introduction

Lymphomatous meningitis (LM) due to primary central nervous system (CNS) lymphoma is an uncommon problem in neurooncology and can occur at time of diagnosis or recurrence. Notwithstanding frequent focal signs and symptoms, LM is a disease affecting the entire neuraxis, and therefore staging and treatment need to encompass all cerebrospinal fluid (CSF) compartments. Central nervous system staging of LM includes contrast agent–enhanced cranial computed tomography (CT) or Gd-enhanced magnetic resonance (MR) imaging, Gd-enhanced spinal MR imaging, CT myelography, and radionuclide CSF flow study. Treatment of LM includes involved-field radiotherapy of bulky or symptomatic disease sites and intra-CSF drug therapy. The inclusion of concomitant systemic therapy can benefit patients with LM and can obviate the need for intra-CSF chemotherapy. At present, intra-CSF drug therapy is confined to three chemotherapeutic agents (methotrexate, cytosine arabinoside, and thiotepa) administered by a variety of schedules either by intralumbar or intraventricular drug delivery. Although treatment of LM is palliative and the expected median survival of patients is 4 to 6 months, it often provides stabilization and protection from further neurological deterioration. In patients with primary CNS lymphoma, CNS prophylaxis has been recommended (using a combination of high-dose systemic chemotherapy and intra-CSF chemotherapy), but the strategy remains controversial because high-dose systemic methotrexate is commonly used as an adjuvant therapy. Patients with primary CNS lymphoma at high risk as defined by positive CSF cytology or neuroradiography consistent with LM may benefit from the inclusion of intra-CSF chemotherapy.

Primary CNS lymphomas are uncommon primary brain tumors that represent 1 to 2% of all brain tumors.[1,4-6,27-30,32,42,44,52-55,61,70] Primary CNS lymphomas occur in both immunocompetent and immunocompromised patients, especially in those who have undergone organ transplantation and in those with acquired immunodeficiency syndrome.[5,70] The clinical presentation of patients with primary CNS lymphomas is a reflection of tumor topography within the CNS and most commonly one of several cerebral syndromes such as raised intracranial pressure, evolving stroke, or encephalopathy.[1,4-6,27-30,32,42,44,52-55,61,70] In approximately one third of patients, however, an atypical presentation occurs, including that of LM.[44,55] Primary CNS lymphoma recurs in the majority of patients, and in 40% of patients when restaging is undertaken following recurrence, LM is shown to be present.[3,16,48]

Incidence of LM

Because the definition of LM and the methods of assessment differ from study to study, defining its incidence in newly diagnosed patients with primary CNS lymphoma is problematic. The authors of the majority of studies have defined LM by a positive CSF cytopathology, which is the traditional method of assessment. The authors of other studies, however, have reported incidences based on CSF flow cytometry, polymerase chain reaction, neuroimaging, or autopsy results as alternative methods of assessment. Another issue that likely affects the variability in incidence encountered between studies is the timing of surgery, volume of the lesion, site of sampling (ventricular or lumbar region), and frequency of CSF assessment. Cerebrospinal fluid sampling and yield of CSF cytology may, in addition, be affected by treatment, and the authors of most studies have not elaborated on how or when CSF sampling is performed.

In studies in which investigators define LM as a positive CSF cytopathological finding, the results are similar.[3,29] Balmaceda and colleagues[3] each reported a prevalence of 27%, whereas other investigators, including Ferreri and colleagues[29] who reported on a larger series of patients, noted a prevalence of LM of 12 to 16%. When other methods of assessment, such as biopsy sampling and MR imaging, are integrated with CSF cytopathological examination, the reported prevalence increases, and in one study of patients with newly diagnosed primary CNS lymphomas it was 42%. The authors of other studies using different modalities, including polymerase chain reaction for a component of immunoglobulin G heavy chain or contrast agent-enhanced brain and spinal imaging alone, have reported lower prevalence values for LM: 13 and 12.5%, respectively.[41,47] Thus, on the basis of published reports the frequency of LM ranges from 12.5 to 42% in patients with newly diagnosed primary CNS lymphomas.

Isolated leptomeningeal relapse is uncommon in patients with primary CNS lymphomas; however, simultaneous disease in the brain and leptomeninges has been reported in up to 40% of patients with primary CNS lymphoma at the time of relapse.[3,5,53]

In summary, LM is sufficiently common that leptomeningeal-directed therapy is indicated as part of the treatment regimen in patients with newly diagnosed primary CNS lymphomas. Leptomeningeal-directed therapy takes several forms: intra-CSF chemotherapy, radiotherapy, or high-dose systemic chemotherapy that in addition treats the leptomeningeal compartment (for example, high-dose intravenous methotrexate).[36]

Clinical Features of LM

Lymphomatous meningitis classically presents with pleomorphic clinical manifestations encompassing symptoms and signs in the following three domains of neurological function: 1) the cerebral hemispheres; 2) the cranial nerves; and 3) the spinal cord and roots. Signs on examination generally exceed the symptoms reported by the patient.[2,11,36,69,71]

The most common manifestations of cerebral hemisphere dysfunction are headache and mental status changes. Other signs include confusion, dementia, seizures, and hemiparesis. These findings often overlap with signs of parenchymal primary CNS lymphomas and therefore the clinical distinction between parenchymal and CSF compartment disease can be challenging. Diplopia is the most common symptom of cranial nerve dysfunction, with the sixth cranial nerve being the most frequently affected, followed by the third and fourth cranial nerves. Trigeminal sensory or motor loss, cochlear dysfunction, and optic neuropathy are also common findings. Spinal signs and symptoms include weakness (lower extremities more often than upper), dermatomal or segmental sensory loss, and pain in the neck, back, or following radicular patterns. Nuchal rigidity is only present in 15% of cases.[2,11,36,69,71]

A high index of suspicion is required to make the diagnosis of LM. The finding of multifocal neuraxis disease in a patient with primary CNS lymphoma is strongly suggestive of LM, but it is also common for patients with LM to present with isolated syndromes such as symptoms of raised intracranial pressure, cauda equina syndrome, or cranial neuropathy.

New neurological signs and symptoms may represent progression of LM but must be distinguished from the manifestations of parenchymal disease, from side effects of chemotherapy or radiotherapy, and, rarely, from paraneoplastic syndromes.

Diagnosis of LM

The most useful laboratory test for diagnosing LM is investigation of the CSF. Abnormalities include increased opening pressure (> 26 mm H_2O), increased leukocytes (> 4/mm^3), elevated protein (> 50 mg/dl), or decreased glucose (< 60 mg/dl), parameters that, although suggestive of LM, are not diagnostic. The presence of malignant cells in the CSF is diagnostic of LM.

In up to 45% of patients with positive CSF cytology (see subsequent discussion), the initial examination will be cytologically negative.[40] The yield is increased to 80% with a second CSF examination, but little benefit is obtained from repeated lumbar punctures after two such procedures.[71] Of note, in a series including lymphomatous and leukemic meningitis reported by Kaplan, et al.,[27] the authors observed the frequent dissociation between CSF cell count and malignant cytology (29% of cytologically positive CSF had concurrent CSF counts of < 4/mm^3).[36] Murray, et al.,[51] showed that CSF levels of protein, glucose, and malignant cells vary at different levels of the neuraxis, even if there is no obstruction of the CSF flow. This finding reflects the multifocal nature of LM and explains why CSF obtained from a site distant to that of the pathologically involved meninges may yield a negative cytology.

Of the 90 patients reported on by Wasserstrom, et al.,[71] a positive CSF cytology in samples obtained from either the ventricles or cisterna magna was noted in 5% of the cases. In a series of 60 patients with LM, positive lumbar CSF cytology at diagnosis, and no evidence of CSF flow obstruction, ventricular and lumbar cytological samples obtained simultaneously were discordant in 30% of cases.[31] The authors observed that in the presence of spinal signs or symptoms the lumbar CSF was more likely to be positive and, conversely, in the presence of cranial signs or symptoms the ventricular CSF was more likely to be positive. Obtaining no CSF sample from a site of symptomatic or radiographically demonstrated disease was found to correlate with false-negative cytological results in a prospective evaluation of 39 patients, as did withdrawing small CSF volumes (< 10.5 ml), delayed processing of specimens, and obtaining fewer than two samples.[35] Even after correcting for these factors, a substantial group of patients remains who have LM and persistently negative CSF cytological findings. Glass,

et al.,[40] reported on a postmortem evaluation in which they assessed the value of premortem CSF cytology. They demonstrated that up to 40% of patients with clinically suspected LM proven at time of autopsy were cytologically negative. This figure increased to greater than 50% in patients with focal LM.

The low sensitivity of CSF cytological examination makes it difficult not only to diagnose LM but also to assess the response to treatment. Biochemical markers, immunohistochemical, and molecular biology techniques applied to CSF have been explored in an attempt to determine a reliable biological marker of disease.

Numerous biochemical markers have been evaluated, but in general their use has been limited by poor sensitivity and specificity.[13] Nonspecific tumor markers such as creatinine-kinase BB isoenzyme, tissue polypeptide antigen, β_2-microglobulin, β-glucoronidase, lactate dehydrogenase isoenzyme-5, and, more recently, vascular endothelial growth factor can be strong indirect indicators of LM, but none is sensitive enough to improve the cytological diagnosis.[65] The use of these biochemical markers can be helpful as adjunctive diagnostic tests and, when followed serially, to assess response to treatment. Occasionally, in patients with clinically suspected LM and negative CSF cytological results, they may support the diagnosis of LM.

Use of monoclonal antibodies for immunohistochemical analysis in LM does not significantly increase the sensitivity of cytological examination alone.[10,33,45,68] However, in LM, antibodies against surface markers can be used to distinguish between reactive and neoplastic lymphocytes in the CSF.

Cytogenetic studies have also been evaluated in an attempt to improve the detection of LM. Flow cytometry and DNA single-cell cytometry, techniques that measure the chromosomal content of cells, and fluorescence in situ hybridization, which detects numerical and structural genetic aberrations as a sign of malignancy, can provide additional diagnostic information, but these modalities still have a low sensitivity.[8,25,56,67] Polymerase chain reaction can establish a correct diagnosis when cytological findings are inconclusive, but the genetic alteration of the neoplasia must be known for it to be amplified with this technique.[42]

In cases in which there is no manifestation of systemic cancer and CSF examinations remain inconclusive, evaluation of a meningeal biopsy specimen can be diagnostic. The yield of this test increases if the biopsy sample is taken from an enhancing region demonstrated on MR imaging.[24]

Magnetic resonance imaging with Gd enhancement is the modality of choice to evaluate patients with suspected leptomeningeal metastasis.[23,59,66] Because LM involves the entire neuraxis, whole-CNS imaging is required in patients considered for further treatment. Both contrast agent-enhanced and unenhanced T_1-weighted sequences, combined with fat suppression T_2-weighted sequences, constitute the standard MR imaging examination. Magnetic resonance imaging has been shown to have a higher sensitivity than cranial contrast medium-enhanced CT scanning in several series and is similar to CT myelography for the evaluation of the spine, but is significantly better tolerated.[12,31,58]

Any irritation of the leptomeninges will result in their enhancement on MR imaging, which is seen as a fine signal intense layer that follows the gyri and superficial sulci. Subependymal involvement of the ventricles often results in enhancement of the ventricles. Some changes such as cranial nerve enhancement and intradural extramedullary enhancing nodules (most frequently seen in the cauda equina) can be considered diagnostic of LM in patients with cancer. Because lumbar puncture itself rarely causes a meningeal reaction leading to dural-arachnoidal enhancement, imaging should be conducted preferably prior to the procedure.[50] The incidence of false-negative results on Gd-enhanced MR imaging remains 30% so that a normal study does not exclude the diagnosis of an LM. In cases involving a typical clinical presentation, however, abnormal results on Gd-enhanced MR imaging alone are adequate to establish the diagnosis of LM.

Radionuclide studies involving either ^{111}Indium-diethylenetriaminepentaacetic acid or 99Tc macroaggregated albumin constitute the technique of choice for evaluating CSF flow dynamics.[14,15,18,22,37,49] Abnormal CSF circulation has been demonstrated in 30 to 70% of patients with LM, with blocks commonly occurring at the skull base, the spinal canal, and over the cerebral convexities. In several clinical series of patients in whom interruption of CSF flow was demonstrated by radionuclide ventriculography, the authors observed decreased survival compared with those in whom CSF flow was normal.[18,37] Involved-field radiotherapy targeting the site of CSF flow obstruction restores flow in 30% of patients with spinal disease and 50% of those with intracranial disease. Reestablishment of CSF flow with involved-field radiotherapy and subsequent intra-CSF chemotherapy led to longer survival, lower rates of treatment-related morbidity, and a lower mortality rate from progressive LM

compared with the group in which there were persistent CSF blocks.[18,37] These findings may reflect the possibility that CSF flow abnormalities prevent homogenous distribution of intra-CSF chemotherapy, resulting in 1) protected sites where the tumor can progress and 2) the accumulation of drug at other sites resulting in neurotoxicity and systemic toxicity. Based on this, many authors recommend that intra-CSF chemotherapy be preceded by a radionuclide flow study and, if a block is found, that radiotherapy be administered in an attempt to reestablish normal flow.[14]

In summary, patients with suspected LM, newly diagnosed primary CNS lymphomas, or recurrent primary CNS lymphomas should undergo evaluation of the CSF compartment to include one or two lumbar punctures, cranial Gd-enhanced MR imaging, spinal Gd-enhanced MR imaging, and a radioisotope CSF flow study to rule out sites of CSF blockage. If cytological findings remain negative and neuroimaging results are not definitive, consideration may be given to ventricular or lateral cervical CSF analysis based on the suspected site of predominant disease. If the clinical scenario or imaging studies are highly suggestive of LM, treatment is warranted despite persistently negative CSF cytological findings.

The treatment of LMs is complicated by the lack of standard therapy, the difficulty of determining response to treatment because of the suboptimal sensitivity of the diagnostic procedures, the fact that most patients die of progressive parenchymal disease, and the fact that most studies of LM are small, nonrandomized, and retrospective. However, it is clear that treatment of LM can provide effective palliation and in some cases result in prolonged survival. Treatment in most cases requires the combination of surgery, radiotherapy, and chemotherapy.

Surgery is used in the treatment of LM for the placement of 1) intraventricular catheters and subgaleal reservoirs for administration of cytotoxic drugs and 2) ventriculoperitoneal shunts in patients with symptomatic hydrocephalus.

Drugs can be instilled into the subarachnoid space by lumbar puncture or via an intraventricular reservoir system. The latter is the preferred approach because it is simpler, more comfortable for the patient, and safer than repeated lumbar punctures. It also results in a more uniform distribution of the drug in the CSF space and produces the most consistent CSF levels. In up to 10% of lumbar punctures the drug is delivered to the epidural space, even if there is CSF return after placement of the needle, and the distribution of the drug has been shown to be better after reservoir-based drug delivery.

The two basic types of reservoirs are 1) the Rickham-style reservoir, a flat rigid reservoir placed over a bur hole, and 2) the Ommaya reservoir, a dome-shaped reservoir that can be easily palpated.[7,57] These reservoirs are generally placed over the right (nondominant) frontal region after making a small C-shaped incision. The catheter is placed in the frontal horn of the lateral ventricle or close to the Monro foramen through a standard ventricular puncture. In most cases, anatomical landmarks suffice, but ultra sonography or CT guidance can be helpful in some situations. It is important to be sure that the tip and the side perforations of the catheter are inserted completely into the ventricle to avoid drug instillation into the brain parenchyma. Correct placement of the catheter should be checked by CT scanning without contrast medium prior to its use for drug administration. This frequently will show a small amount of air in both frontal horns.

Lymphomatous meningitis often causes communicating hydrocephalus leading to symptoms of raised intracranial pressure. Relief of sites of CSF flow obstruction with involved-field radiation should be attempted to avoid the need for placing a CSF shunt. If hydrocephalus persists, a ventriculoperitoneal shunt should be placed to relieve the pressure because relief of pressure often results in clinical improvement. If possible, an in-line on/off valve and reservoir should be used to permit the administration of intra-CSF chemotherapy, although some patients cannot tolerate having the shunt turned off to allow the circulation of the drug.

Finally, in patients with a persistent blockage of ventricular CSF flow, a lumbar catheter and reservoir can be used in addition to a ventricular catheter, to allow treatment of the spine with intra-CSF chemotherapy (although as discussed earlier, cases involving postirradiation persistent CSF flow blocks are probably best managed using supportive care alone).

Radiotherapy Management

Radiotherapy is used in the treatment of LM for several reasons: 1) palliation of symptoms, such as a cauda equina syndrome, 2) to decrease space-occupying disease such as large-volume subarachnoid metastases, and 3) to correct CSF flow abnormalities demonstrated by radionuclide ventriculography. Patients may exhibit significant symptoms despite the absence of imaging evidence of space-occupying disease and still benefit from radiotherapy. For example, patients with low-back pain and

leg weakness should be considered for radiotherapy of the cauda equina, and those with cranial neuropathies should be offered whole-brain or base skull radiotherapy.

Radiotherapy of large-volume disease is indicated because intra-CSF chemotherapy is limited by diffusion to 2 to 3 mm penetration into tumor nodules. In addition, involved-field irradiation can correct CSF flow abnormalities, and this has been shown to improve patient outcome, as previously discussed. Whole-neuraxis radiotherapy is rarely indicated in the treatment of LM from solid tumors because it is associated with significant systemic toxicity (severe myelosuppression and mucositis, among other complications) and is not curative.

Chemotherapy Management

Chemotherapy is the only modality that can treat the entire neuraxis and can be administered systemically or intrathecally.[11,36,60,63,70] The most effective drug used in patients with newly diagnosed primary CNS lymphoma is high-dose methotrexate.[1,4-6,27-30,32,42,44,52-54,55,61,70] When this drug is administered in gram quantities (high dose), cytotoxic CSF levels are achieved. Following a single dose of intravenous methotrexate at 8 g/m^2, CSF methotrexate levels greater than 1.0 µM are obtained and sustained for 24 to 48 hours.[36] In a study by Glantz and colleagues[36] of 16 patients with solid tumors and leptomeningeal metastases, methotrexate was administered intravenously at 8 g/m^2 over 4 hours and accompanied by serial sampling of CSF and blood.[21] In this study, there was also a parallel group of patients who received intra-CSF methotrexate at a standard dose and schedule. After a single intravenous dose, methotrexate levels of 1.0 µM were maintained in the CSF for, on average, 48 hours and 0.1 µM for up to 93 hours. In the patients who received a single intra-CSF methotrexate dose, levels of 1.0 µM were maintained for 35 to 48 hours and 0.1 µM levels were maintained for approximately 57 hours. Therefore, on these drug schedules and at these doses, the duration of cytotoxic drug exposure in the CSF was similar in patients who received intravenous or intra-CSF methotrexate.

The treatment of concomitant LM in the setting of recurrent parenchymal primary CNS lymphomas is challenging. Most systemic chemotherapy treats LM inadequately due to the insufficient CSF drug levels as seen in cases in which temozolomide, PCV (procarbazine, CCNU, and vincristine), rituximab, or topotecan are used. Exceptions are seen when using high-dose methotrexate, cytosine arabinoside, or thiotepa—chemotherapy agents with demonstrated activity against leptomeningeal metastases. Alternatively, intraventricular chemotherapy can be used, which, although limited to three agents (methotrexate, cytosine arabinoside, and thiotepa), has demonstrated activity and palliative benefit in patients with LM.[16,26,71] However, intra-CSF chemotherapy is primarily effective against small tumor burden and disease involving the CSF and 1 to 2 mm of the leptomeningeal surface.[16,26,71] Larger subarachnoid or parenchymal tumors are ineffectively treated by intra-CSF chemotherapy and, if present, require concomitant systemic chemotherapy or involved-field radiotherapy.[16,17,26,71]

The authors of a retrospective study of 14 patients with recurrent primary CNS lymphomas complicated by LM compared two approaches: seven patients received intraventricular chemotherapy, systemic chemotherapy, and involved-field radiotherapy and seven other patients received high-dose methotrexate or cytarabine systemic chemotherapy and involved-field radiotherapy.[20] Both patient groups were similar in age and prior adjuvant therapies. No significant difference was seen in outcome defined by the percentage of patients with disease-free survival (28%), death due to progressive primary CNS lymphomas (72%), and median survival in patients dying of primary CNS lymphomas (range 5-6 months). Furthermore, in disease-free survivors the incidences of clinically apparent and clinically inapparent imaging-documented leukoencephalopathy were comparable in both treatment groups. Toxicity differed between the treatment groups: in patients who underwent intraventricular chemotherapy, treatment-related aseptic meningitis manifested, whereas mucositis and myelosuppression was seen in patients treated with high-dose methotrexate or cytosine arabinoside.

These results suggest that either treatment approach is valid and equally efficacious. Therefore, the decision of how to treat patients with recurrent primary CNS lymphomas complicated by LM includes two comparable regimens that differ primarily in the use of an intraventricular catheter and reservoir system and frequent outpatient treatments compared with a 3- to 4-day period of hospitalization twice per month. In addition to these considerations, a clear difference exists between toxicity with these treatment approaches. Consequently, recurrent primary CNS lymphomas complicated by LM can be effectively treated by either intraventricular chemotherapy or high-dose systemic chemotherapy using either methotrexate or cytosine arabinoside. Approximately one quarter of patients can be expected to be long-term survivors following treatment; however, 50% will have symptomatic treatment-related leukoencephalopathy.

Notwithstanding the aforementioned study, intra-CSF chemotherapy is the mainstay of treatment for LM. Retrospective analysis or comparison with historical series suggests that CSF chemotherapy improves the outcome of patients with LM.[9,16,34,38,39,43,46,64,71] It is noted, however, that the authors of most series will exclude patients who are too sick to receive any treatment, which may be as many as one third of patients with LM.[38,39] Three agents are routinely used: methotrexate, cytarabine (including extended-release liposomal cytarabine or DepoCyt), and thiotepa. No difference in response has been seen when comparing single-agent methotrexate with thiotepa or when using multiple-agent (methotrexate, thiotepa, and cytarabine or methotrexate and cytarabine) compared with single-agent methotrexate treatment. A sustained-release form of cytarabine (DepoCyt) results in cytotoxic cytarabine levels in the CSF for greater than or equal to 10 days; when given bimonthly and compared with biweekly methotrexate, it resulted in greater duration before neurological progression in patients with LM.[38] Furthermore, the data pertaining to the quality of life and cause of death favored DepoCyt over methotrexate. These findings have been confirmed in a study of LM and in an open-label study, suggesting that DepoCyt should be considered the drug of first choice in the treatment of LM.[39,46]

Complications of intra-CSF chemotherapy include those related to the ventricular reservoir and those related to the chemotherapy agent(s) administered.[19,64] The most frequent complications of ventricular reservoir placement are malposition (range of reported rates 3-12%), obstruction, and infection (usually skin flora). Cerebrospinal fluid infection occurs in 2 to 13% of patients undergoing intra-CSF chemotherapy. Patients with CSF infection commonly present with headache, changes in neurological status, fever, and malfunction of the reservoir. Cerebrospinal fluid pleocytosis is commonly encountered. The most frequently isolated organism is *Staphylococcus epidermidis*. Treatment requires intravenous administration of antibiotics with or without oral and intraventricular agents. Some authors have advocated the routine removal of the ventricular reservoir, whereas others believe that removal of the device should be reserved for cases in which antibiotic therapy does not resolve the infection. Routine culturing of CSF samples is not recommended because of the high rate of contamination with skin flora in the absence of infection. Myelosuppression can occur after administration of intra-CSF chemotherapy agents, and it is recommended that folinic acid rescue (10 mg every 6 hours for 24 hours) be given orally after the administration of methotrexate to avoid this complication. Chemical aseptic meningitis occurs in nearly 50% of patients treated by intra-CSF administration, and its symptoms manifest as fever, headache, nausea, vomiting, meningismus, and photophobia. In most patients, this inflammatory reaction can be treated in the outpatient setting with oral antipyretic, antiemetic, and corticosteroid agents. Rarely, treatment-related neurotoxicity occurs and can result in a symptomatic subacute leukoencephalopathy or myelopathy. In patients with LM and prolonged survival, however, the combination of radio- and chemotherapy frequently results in a late-onset leukoencephalopathy evident on imaging studies and occasionally causing symptoms.[34,38,39,43,46,62]

The rationale for giving intra-CSF chemotherapy is based on the presumption that most chemotherapeutic agents, when administered systemically, have poor CSF penetration and do not reach therapeutic levels. Exceptions to this would be systemic high-dose methotrexate, cytarabine, and thiotepa, all of which result in cytotoxic CSF levels. Their systemic administration is limited, however, by systemic toxicity and by the difficulty of integrating these regimens into other chemotherapeutic programs being used to manage a patient's systemic disease. Additionally, in patients with recurrent primary CNS lymphomas and previous treatment with high-dose methotrexate, alternative systemic therapies are used without compelling evidence of CSF penetration or the ability to eradicate the CSF compartment. Some authors have argued that intra-CSF chemotherapy does not add to improved outcome in the treatment of LM, because systemic therapy can reach the subarachnoid deposits through tumor vascular supply.[62]

Nonetheless, intrathecal chemotherapy remains the preferred treatment route for LM at this time. New intra-CSF drugs are being explored to try to improve efficacy, including mafosphamide, diaziquone, topotecan, interferon-α, etoposide, rituximab, and temozolomide. Gene therapy and immunotherapy using interleukin-2 and interferon-α, ^{131}I-radiolabeled monoclonal antibodies are other modalities being explored in clinical trials.

Not all patients with LM are candidates for the aggressive treatment outlined in this review. Most authors agree that combined-modality therapy should be offered to patients with a life expectancy greater than 3 months and a Karnofsky Performance Scale score greater than 60.

Certain supportive care measures should be offered to every patient, regardless of whether they receive LM-directed therapy. These therapies include anticonvulsant agents for seizure control (seen in 10-15% of patients with LM), adequate analgesia with opioid drugs, as needed, and antidepressant and anxiolytic medications if necessary. Corticosteroid agents are of limited use in LM-related neurological symptoms but can be useful to treat vasogenic edema associated with intraparenchymal or

epidural metastases or for the symptomatic treatment of nausea and vomiting together with routine antiemetic agents. Decreased attention and somnolence secondary to whole-brain radiotherapy can be treated with psychostimulants.

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Abbreviation Notes

CNS = central nervous system; CSF = cerebrospinal fluid; CT = computed tomography; LM = lymphomatous meningitis; MR = magnetic resonance.

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Neurosurg Focus. 2006;21(5)