Background: Neoplastic meningitis, also known as leptomeningeal disease, affects the entire neuraxis. The clinical manifestations of the disease may affect the cranial nerves, cerebral hemispheres, or the spine. Because of the extent of disease involvement, treatment options and disease staging should involve all compartments of the cerebrospinal fluid (CSF) and subarachnoid space. Few studies of patients with primary brain tumors have specifically addressed treatment for the secondary complication of neoplastic meningitis. Therapy for neoplastic meningitis is palliative in nature and, rarely, may have a curative intent.

Methods: A review of the medical literature pertinent to neoplastic meningitis in primary brain tumors was performed. The complication of neoplastic meningitis is described in detail for the various types of primary brain tumors.

Results: Treatment of neoplastic meningitis is complicated because determining who should receive aggressive, central nervous system (CNS)–directed therapy is difficult. In general, the therapeutic response of neoplastic meningitis is a function of CSF cytology and, secondarily, of the clinical improvement in neurological manifestations related to the disease. CSF cytology may manifest a rostrocaudal disassociation; thus, consecutive, negative findings require that both lumbar and ventricular cytological testing are performed to confirm the complete response. Based on data from several prospective, randomized trials extrapolated to primary brain tumors, the median rate of survival for neoplastic meningitis is several months. Oftentimes, therapy directed at palliation may improve quality of life by protecting patients from experiencing continued neurological deterioration.

Conclusions: Neoplastic meningitis is a complicated disease in which response to therapy varies by histology. Thus, survival rates after CNS-directed therapy will differ by the underlying primary tumor. Optimal therapy of neoplastic meningitis is poorly defined, and few guidelines exist to guide clinicians on the most appropriate choice of therapy.

Introduction
Neoplastic meningitis is a disease that affects the cerebral hemispheres, the spine, and the cranial nerves. All cerebrospinal fluid (CSF) compartments (ventricles, basal cisterns, cerebral and spinal subarachnoid space) need to be assessed during staging and considered with respect to treatment. Most often, treatment involves radiotherapy and the intra-CSF administration of chemotherapy. For many patients, concomitant, systemic therapy is required because of systemic tumor recurrence. Therapeutic agents for intra-CSF administration include cytosine arabinoside, liposomal cytarabine, methotrexate, rituximab, thiotepa, and trastuzumab.

Chamberlain et al1 proposed an evaluation for assessing response in neoplastic meningitis that includes CSF cytology/flow cytometry, radiographic evaluation, and a standardized neurological examination. The proposal (Response Assessment in Neuro-Oncology) recommended that CSF analysis be performed for all patients, as well as complete, contrast-enhanced neuraxis magnetic resonance imaging (MRI), and, when the intra-CSF administration of therapy is planned, radioisotope CSF flow studies should be obtained.1 A standardized instrument was created to assess a neurological examination that does not require neurological consultation.1 Because the majority of radiographic lesions that occur in the setting of neoplastic meningitis cannot be measured, the working group proposed that clinicians use a novel, radiological response scorecard to grade neuroimaging as improved, stable, or progressive. Isolated progression based on radiographic evidence was defined as sufficient to determine disease progression of neoplastic meningitis.1 The proposal by Chamberlain et al1 recognizes these instruments are novel and will require validation in prospective clinical studies.

From the Lynn Cancer Institute (SC), Marcus Neuroscience Institute, Boca Raton, Florida, Damlo Dose (SD), and Seattle Cancer Care Alliance (MCC), Cascadian Therapeutics, Seattle, Washington.

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Address correspondence to Sajeel Chowdhary, MD, Marcus Neuroscience Institute, 800 Meadows Road, First Floor, Boca Raton, FL 33486. E-mail: SChowdhary@brrh.com.

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trials of neoplastic meningitis.

A paucity of literature exists relating to the treatment of primary brain tumors and the co-occurrence of neoplastic meningitis. However, general principles have been established regarding neoplastic meningitis. Therapy for neoplastic meningitis is palliative in nature with rare curative intent. Few guidelines exist for the treatment and response evaluation of neoplastic meningitis. The current effort reviewed the medical literature pertinent to neoplastic meningitis in primary brain tumors to assist clinicians in understanding existing therapies for and the evaluation of neoplastic meningitis.

Clinical Presentation

The classic presentation of neoplastic meningitis includes pleomorphic clinical manifestations relating to neurological function in the spinal cord and its exiting nerve roots, the cerebral hemispheres, and the cranial nerves. Typically, a neurological examination will uncover additional signs and symptoms beyond what patients have reported.

Changes in mental status and headache are the most common manifestations of dysfunction in the cerebral hemisphere, although confusion, dementia, hemiparesis, and seizure can occur. Dysfunction of the cranial nerves, the most common being cranial nerve VI, can manifest as diplopia or trigeminal sensory or motor loss; optic neuropathy and cochlear dysfunction are also common. Spinal manifestations can include lower- and upper-extremity weakness, segmental/dermatomal sensory loss, pain, and nuchal rigidity.

Clinicians should have a high index of suspicion to make the diagnosis of neoplastic meningitis. Discovery of multifocal neuraxis disease in a patient with malignancy is suggestive of neoplastic meningitis; however, patients with neoplastic meningitis also commonly present with isolated syndromes, including cranial neuropathy and cauda equina syndrome.

New manifestations of a neurological nature may represent disease progression; however, the clinician must distinguish these from the signs and symptoms of parenchymal disease and treatment-related adverse events.

Diagnosis

Examination of the Cerebrospinal Fluid

Examination of the CSF is considered the most useful laboratory study to aid in the diagnosis of neoplastic meningitis. Abnormalities that clinicians should consider on the examination of CSF include increased leukocyte count, elevated opening pressure, decreased glucose level, or elevated protein level; however, such values are only suggestive and are not diagnostic of neoplastic meningitis. Although the presence of malignant cells in the CSF is diagnostic for the disease, determination of specific histology is currently not possible.

Nearly one-half of patients with positive CSF cytology will have cytologically negative findings on an initial CSF examination. That number increases to 80% when repeat CSF examination is performed; however, little benefit is achieved from more than 2 lumbar punctures.

Wasserstrom et al reported on 90 patients with carcinomatous meningitis, 5% of whom had positive results on CSF cytology from either the cisterna magna or ventricles. Chamberlain et al found that positive findings on lumbar CSF cytology at diagnosis, absent CSF flow obstruction, and simultaneously obtained ventricular and lumbar cytology samples were discordant in 30% of cases. When spinal manifestations were present, the authors discovered that lumbar CSF cytology was more likely to be positive; alternatively, ventricular CSF cytology was more likely to be positive when cranial signs or symptoms were present. Not obtaining CSF from a site of radiographically demonstrable or symptomatic disease was associated with false-negative results on cytology in their prospective evaluation of 39 patients, as did withdrawing less than 10.6 mL of CSF, taking fewer than 2 samples, and delaying the processing of specimens. After the authors corrected for these factors, they discovered several of their study patients with neoplastic meningitis still had persistently negative findings on CSF cytology.

Nearly 40% of cases with clinically suspected neoplastic meningitis proven at the time of autopsy are cytologically negative, according to a study by Glass et al. This number was higher than 50% in patients with focal neoplastic meningitis.

Low sensitivity rates of CSF cytology make diagnosing neoplastic meningitis and assessing treatment response difficult. Immunohistochemistry, molecular biology techniques, and several biochemical markers have been explored to discern a reliable biological marker of disease; however, in general, use of biomarkers has been limited by poor rates of specificity and sensitivity. Using monoclonal antibodies for the analysis of immunohistochemistry in the setting of neoplastic meningitis does not significantly increase the sensitivity rate of cytology alone. However, for cases of leukemia and lymphoma, antibodies against surface markers can distinguish between neoplastic and reactive lymphocytes in the CSF.

Researchers have studied the use of cytogenetics to help improve the rate of diagnostic accuracy for neoplastic meningitis. Additional diagnostic information may be gained through the use of flow/DNA single-cell cytometry, chromosomal measurements, and fluorescence in situ hybridization, which can detect numerical and structural genetic aberrations as signs of malignancy; however, these methods still have low rates of sensitivity. When results from cytology are inconclusive, the clinician may consider use of polymerase
These results suggest that the use of rare cell-capture technology is beneficial for diagnosing neoplastic meningitis in patients with epithelial tumors, which constitute the majority of solid tumors in adults. The researchers detected tumor cells in the CSF and whole blood by multiparameter flow cytometry using an EpCAM antibody. They reported sensitivity and specificity rates of 100% each for the flow cytometry assay when diagnosing neoplastic meningitis, whereas the sensitivity rate was 62% for CSF cytology. Biochemical parameters and cell counts in the CSF were abnormal in all patients studied with neoplastic meningitis. The results suggest that CSF cytology is inferior to EpCAM-based flow cytometry assay for diagnosing neoplastic meningitis in patients with an epithelial tumor who have clinically suspicious neoplastic meningitis and inconclusive findings on MRI.

Nayak et al reported on using rare cell-capture technology for diagnosing neoplastic meningitis from solid tumors by identifying circulating tumor cells (CTCs) in the CSF. The researchers found CTCs in 16 patients. A false-positive result was reported in 1 patient; however, lumbar puncture was performed 6 months later in that patient, who then met the criteria for neoplastic meningitis. The researchers reported that CSF CTCs were absent in the entire control population. Sensitivity rates for rare cell-capture technology, conventional cytology, and MRI were 100%, 67%, and 73%, respectively. Thus, these results suggest that rare cell-capture technology is an accurate, novel method that can detect neoplastic meningitis in solid tumors. The authors suggest that this method could provide clinicians with earlier diagnostic confirmation, thereby sparing patients from undergoing repeat lumbar punctures.

Magbanua et al isolated CTCs derived from the CSF in 15 study patients with metastatic breast cancer who were also diagnosed with neoplastic meningitis. The researchers performed genomic profiling in 87% of the patients. Results of copy number analysis in CTCs revealed the presence of CTCs consistent with their malignant origin and genomic alterations commonly observed in primary breast cancer. In 6 patients, the researchers compared CTCs with corresponding, archival primary tumors and discovered divergence in the clonal relationships. This type of isolation methodology and molecular CTC analysis added to our understanding of these malignant cells. Future functional and genomic analyses could help determine the mechanisms tumor cells use to metastasize to the central nervous system (CNS). Lv et al also reported on detecting tumor cells in the CSF through combined immunofluorescence in situ hybridization. The study involved 24 patients (n = 16 with neoplastic meningitis from lung cancer, n = 8 without CNS malignancy). The researchers compared the CTCs in the CSF between these 2 patient groups. Rates of diagnostic sensitivity, specificity, and effectiveness were 75%, 100%, and 83%, respectively. Negative and positive predictive values were 67% and 100%, respectively. Findings from Lv et al suggest that value may exist in detecting CTCs in the CSF via combined immunofluorescence in situ hybridization for diagnosing meningeal metastasis in select primary cancers.

Pentsova et al reported on sequencing 341 genes associated with cancer in cell-free DNA from CSF. The researchers obtained CSF samples through routine lumbar puncture in 53 patients with cancer and known or suspected CNS involvement. They detected somatic alterations in 50% of patients with primary brain tumors, 63% of patients who had CNS metastases of solid tumors, and in 0% of cases without CNS involvement. The researchers reported that, among the patients studied with glioma, which is the most common malignant primary brain tumor in adults, their examination of cell-free DNA revealed patterns of tumor evolution, including mutations associated with temozolomide. Thus, they concluded that CSF can harbor clinically relevant genomic alterations in patients with CNS-associated cancers. They also suggest that “liquid biopsies” could be used to monitor tumor evolution and treatment response.

In cases for whom no evidence exists of systemic cancer and findings on CSF examination are inconclusive, meningeal biopsy may be diagnostic. The yield of this test increases if the biopsy specimen is obtained from an enhancing region seen on MRI. Most often a posterior fossa or pterional surgical approach is utilized.

**Neuroradiographical Data**

Gadolinium-enhanced MRI is the technique of choice for the evaluation of suspected leptomeningeal metastasis. Neoplastic meningitis involves the entire neuraxis; therefore, the clinician is required to obtain imaging of the entire CNS in patients who are candidates for treatment. T1-weighted sequences, with and without contrast, in combination with fat-suppression, and T2-weighted sequences are considered the standard imaging modalities in this clinical setting. MRI has been shown to have higher rates of sensitivity than cranial, contrast-enhanced computed tomography; its sensitivity is also similar to computed tomographic myelography for evaluating the spine, but it is a logistical-
ly simpler and better tolerated modality.28-30
Tumors involving the leptomeninges can be visualized on enhanced MRI as a fine, signal-intense layer following the superficial sulci and gyri. Subependymal ventricular involvement can also result in ventricular enhancement. Several changes seen on MRI, including enhancement of cranial nerves and intradural extramedullary enhancing nodules, may be diagnostic of neoplastic meningitis in patients with cancer.31-33 Rarely, lumbar puncture can cause a meningeal reaction, which can then lead to dural-arachnoidal enhancement; thus, it is preferred that imaging be obtained prior to performing lumbar puncture.35-35 Gadolinium-enhanced MRI has a 30% rate of false-negative findings, so normal imaging findings cannot exclude the diagnosis of neoplastic meningitis. Alternatively, in patients with typical clinical presentations, abnormal findings seen on gadolinium-enhanced MRI are adequate to establish the diagnosis.35-35

Types of Primary Brain Tumors

Glioma
The management of leptomeningeal gliomatosis and gliomas can be challenging to the clinician because neurological function will be compromised in most cases as a result of treatment and of the topography of the primary tumor.36-40

Most epidemiological research on leptomeningeal gliomatosis is based on autopsy reports.31-44 Erlich and Davis41 reviewed the autopsy results of 25 patients with glioblastoma; of those, examination of the spinal cord was performed in 20 cases. Five cases had evidence of leptomeningeal gliomatosis.31 Yung et al42 reviewed the autopsy findings of 52 patients with high-grade glioma; of those, evidence of leptomeningeal gliomatosis was seen in 11 patients. Eight cases were diagnosed antemortem by positive CSF cytology.42 In an antemortem series, Vertosick and Selker43 reviewed cases in which leptomeningeal gliomatosis was diagnosed based on neuroradiographical imaging findings, not on CSF cytology. They found that leptomeningeal gliomatosis occurred in 2% of cases.42

Awad et al44 reported on 13 patients with leptomeningeal gliomatosis and high-grade glioma, 8 of whom had symptoms prior to their death that were consistent with leptomeningeal gliomatosis. Leptomeningeal gliomatosis was a preterminal event in all patients studied. Reporting on 51 autopsies performed on patients with glioblastoma, Onda et al45 demonstrated evidence of leptomeningeal gliomatosis in 27% of cases. A report of 11 patients with high-grade glioma and leptomeningeal gliomatosis was published by Grant et al,46 who reported that the diagnoses were made antemortem. In 3 cases, leptomeningeal gliomatosis was found at the time of initial tumor presentation. They also found that, among patients previously diagnosed with and who received treatment for anaplastic astrocytoma or glioblastoma, therapy directed at leptomeningeal gliomatosis had little effect.46 In patients with high-grade glioma, evidence of leptomeningeal gliomatosis on autopsy is far more likely than clinically evident leptomeningeal gliomatosis, possibly because discrepancies in antemortem and postmortem diagnoses are difficult to interpret.44-50

Witham et al47 reported on 14 patients with leptomeningeal gliomatosis (n = 5 anaplastic astrocytoma, n = 9 glioblastoma) who were treated with the intra-CSF administration of thiotepa. Of those with high-grade glioma, leptomeningeal gliomatosis was the presenting symptom in 3.47 Five patients had clinical manifestations associated with leptomeningeal gliomatosis.47 Among the 8 patients for whom CSF samples were obtained and examined, CSF cytology was not obtained in 6 and the results were positive in 2.47 Subependymal disease was sufficient to diagnose leptomeningeal gliomatosis per the neuroradiographical criteria used in the study.47

Overall median survival rates have been reported to be 19 months for patients with anaplastic astrocytoma and 10 months for those with glioblastoma.48-50 Patients with high-grade glioma and leptomeningeal gliomatosis defined by clinical manifestations, positive neuroradiographical findings, and positive results on CSF cytology reportedly respond poorly to aggressive, multimodal therapy.48-50 Median survival after the diagnosis of leptomeningeal gliomatosis is made has been reported to be similar to that of neoplastic meningitis secondary to systemic solid cancers.48-50 With regard to neoplastic meningitis, a paucity of evidence suggests that one intra-CSF chemotherapy agent is superior to another or even when used in combination.48-50 Furthermore, many patients may succumb to complications secondary to leptomeningeal gliomatosis, not as a result of primary cancer progression.48-50

Therapy for neoplastic meningitis is multimodal, as approximately two-thirds of patients require radiotherapy for symptomatic or neuroradiographical bulky subarachnoid disease, and approximately one-third require systemic chemotherapy for the progression of their primary tumor.48-50 Therefore, standard management options for carcinomatous meningitis involve treatments such as radiotherapy, systemic chemotherapy, and the intra-CSF administration of chemotherapy. Because neoplastic meningitis variably and pleiomorphically affects the entire neuraxis, combination therapies are used and, thus, it becomes difficult to ascertain benefit to any specific therapy.48-50

Even though modest rates of treatment-related toxicity have been observed in several studies, limited survival rates and poor therapeutic responses suggest that a less-aggressive approach may be justified in patients with leptomeningeal gliomatosis and high-grade cancer.
glioma.\textsuperscript{51-62} Combining palliative care involving radiotherapy directed to the symptomatic disease site and simple systemic chemotherapy regimens could be, in theory, less invasive and as effective as an aggressive, multimodal approach. However, such patients may still benefit from enrolling in clinical trials designed to explore novel treatment approaches to leptomeningeal gliomatosis.\textsuperscript{51-62}

**Meningioma**

Meningiomas mostly occur in middle- or older-aged adults and have a female predominance; most meningiomas are benign, whereas few cases are atypical or malignant (6%–15% and 2%, respectively).\textsuperscript{63-66} Many patients diagnosed with this extra-axial brain tumor elect to undergo surgery for its removal and are advised to do so based on the presence of neurological symptoms.\textsuperscript{63-66} Often complete surgical resection is curative; for cases of incomplete resection or in patients with recurrent tumors not previously irradiated, radiotherapy is appropriate.\textsuperscript{63-66} Conventional external beam radiotherapy or stereotactic radiotherapy may be considered, with stereotactic radiotherapy being increasingly utilized. In unresectable cases or when the disease has failed to respond to surgery or radiotherapy, immunotherapy may be considered. Rarely, meningiomas may metastasize, most often to extraneural sites such as the cervical lymph nodes or lungs.\textsuperscript{63-66}

Metastasis is commonly associated with World Health Organization grade 2 (aggressive) or 3 (malignant) disease, occurring at a rate of up to 25%; however, the risk of dissemination into the CSF is unclear.\textsuperscript{67-70} Aside from angiogenic inhibitors, few chemotherapy agents have demonstrated activity against recurrent meningiomas, thus complicating therapeutic options for these already complex cases. Some authors have reported on patients being treated with multimodal therapy, including systemic and regional chemotherapy and involved-field radiotherapy to sites of symptomatic disease within the spine; however, despite such an approach, median survival has been reported to be approximately 6 months.\textsuperscript{70-72} Meningiomas mostly metastasize by the hematological route, with only occasional CSF dissemination. Multifocal meningiomas may reflect an instance of CSF dissemination. No agents are approved for the treatment of refractory meningioma, so effective chemotherapy agents are an unmet need.\textsuperscript{72,74}

**Primary Central Nervous System Lymphoma**

Primary CNS lymphoma (PCNSL) is a disease that largely involves the brain.\textsuperscript{75} The leptomeninges may be involved in the initial presentation and during disease recurrence, although isolated leptomeningeal disease is rare in patients with PCNSL.\textsuperscript{75}

Korfel et al\textsuperscript{76} described PCNSL as a rare, diffuse large B-cell lymphoma originating within the CNS. Its overall incidence has been increasing, and this is particularly true among the elderly and those with compromised immune systems.\textsuperscript{77} Optimal treatment is relatively unknown because of too few adequately sized trials. Initially, most patients receive high-dose, methotrexate-based chemotherapy alone, because whole-brain radiotherapy given at standard doses is associated with neurological toxicity in these patients and does not have a survival benefit.\textsuperscript{76}

Approximately 10% of patients with PCNSL have positive findings by CSF cytology, and an additional 15% have neuropathology or demonstrable disease by neuroradiography consistent with leptomeningeal spread. In either of these instances, these findings complement positive findings by CSF cytopathy and are indicative of lymphomatous meningitis.\textsuperscript{77-86} A large series by Ferreri et al\textsuperscript{75} reported that the prevalence rate was 16%, whereas Balmaceda et al\textsuperscript{81} reported on data that supported a rate of 26%. Other studies indicate an even lower prevalence rate of 13%.\textsuperscript{78-80,82-85} These rates suggest that many patients have combined brain and leptomeningeal disease and that PCNSL is frequently associated with lymphomatous meningitis.\textsuperscript{75,77-86} Fischer et al\textsuperscript{87} examined the CSF samples from 116 patients with compromised immune systems and newly diagnosed PCNSL. In this prospective, multicenter study, lymphoma cells were found in 18% of the samples, CSF pleocytosis in 36%, and elevated levels of protein in 65%.\textsuperscript{94} The researchers reported that pleocytosis correlated with positive findings on cytology, whereas an elevated protein level in the CSF did not.\textsuperscript{97}

Lymphomatous meningitis is not rare in cases of PCNSL, so leptomeningeal and CSF-directed compartmental therapy (craniospinal irradiation, high-dose systemic chemotherapy [methotrexate, cytarabine, thiopeta], intrathecal chemotherapy) can be administered in select patients with newly diagnosed PCNSL. Methotrexate given at high doses is the most effective drug for newly diagnosed PCNSL. When methotrexate is administered at high levels, cytotoxic CSF levels can be achieved.

In the large, multicenter study of 370 patients with PCNSL conducted by Ferreri et al,\textsuperscript{75} the benefit of adjuvant high-dose methotrexate in combination with or without intrathecal chemotherapy was studied. However, no survival benefit was demonstrated with the addition of the intra-CSF administration of chemotherapy. Furthermore, the study reported that intrathecal chemotherapy had no impact on the recurrence rate or meningeal relapse. These findings were also true for patients with positive CSF cytology findings at diagnosis.\textsuperscript{75} Thus, the study results suggest that high-dose methotrexate systemic regimens obviate the need for intra-CSF administration of chemotherapy in patients with leptomeningeal disease.\textsuperscript{78-85}

Glantz et al\textsuperscript{88} reported on 16 patients with solid
tumors and leptomeningeal metastases. Patients were given intravenous methotrexate 8 g/m² within 4 hours, after which serial sampling of their CSF and blood was performed. These patients were compared with a parallel group, who were administered intra-CSF methotrexate according to its standard dosing schedule. In the patients who received the drug intravenously, 1.0 μM and 0.1 μM levels of methotrexate were maintained in the CSF for approximately 48 and 93 hours, respectively. In those receiving a single intrathecal dose, 1.0 μM and 0.1 μM levels of methotrexate were maintained for approximately 48 and 57 hours, respectively. Therefore, the authors concluded that the duration of cytotoxic drug exposure in the CSF was similar among the 2 groups.

Ependymoma

CSF dissemination occurs in up to 12% of all cases of intracranial ependymomas, with its highest frequency occurring in infratentorial anaplastic ependymomas. Albeit a small but measurable risk, CSF dissemination may occur in any patient newly diagnosed with ependymoma; thus, patients should be evaluated for extent of the disease. Such an examination occurs most often after surgery and should include obtaining CSF cytology and craniospinal MRI. Staging can be utilized to stratify patients into those with (stage M1) or without CSF metastasis (stage M0) as well as those with residual disease or without following surgery. Metastasis and residual disease are the most important clinical parameters that affect patient outcomes.

In a retrospective review, Fangusaro et al evaluated the incidence rate of metastatic disease, prognostic factors, and survival outcomes in 61 patients with intracranial ependymoma. Bulky metastatic disease observed on postcontrast spine MRI occurred in 10% of the study population. They found that none of the patients whose findings on spine MRI were negative had positive findings on lumbar CSF cytology, thus highlighting the rarity of microscopic metastatic disease observed on lumbar CSF cytology alone. These results suggest that lumbar CSF cytology may not be useful when negative findings are observed on postcontrast spine MRI.

The first treatment of choice for ependymomas is surgical resection because it is the most important covariant affecting rates of overall and progression-free survival (PFS). Following surgery, the second most frequently used adjuvant treatment is radiotherapy, even with the general medical consensus that ependymomas are resistant to radiotherapy and in the absence of randomized clinical trials suggesting any benefit for completely resected tumors. Furthermore, no data indicate whether a dose-response relationship exists in ependymomas; thus, total tumor dose varies. CSF spread is theoretically possible and the volume of brain requiring treatment with radiotherapy has been controversial. Notwithstanding the initial enthusiasm for craniospinal irradiation, several study authors have suggested that use of limited-field radiotherapy for M0 disease may be appropriate, thereby reserving craniospinal irradiation for M1+ disease regardless of tumor histology and, according to others, for anaplastic ependymomas in the infratentorial compartment.

Robertson et al studied the role of adjuvant chemotherapy after surgery and craniospinal irradiation in a prospective trial of 32 children. The study patients were newly diagnosed with intracranial ependymoma. They found that the volume of residual disease and extent of surgical resection predicted the rate of PFS, but that chemotherapy, regardless of the regimen, did not impact PFS. They reported that overall survival and 5-year PFS rates were 64% and 50%, respectively. A total of 71% of relapses observed were related to failures of local treatment and 21% to concurrent distant and local metastasis to the CNS. Approximately 7% were related to isolated metastatic relapse but occurred only in cases of metastatic disease at diagnosis. Similar outcomes were seen among patients receiving craniospinal irradiation or involved-field radiotherapy. Robertson et al concluded that craniospinal irradiation should be confined to patients with documented disseminated neuraxis disease. Whether the intra-CSF administration chemotherapy will replace craniospinal irradiation in patients who present with metastatic disease seems unlikely because rates of survival have not improved with the use of adjuvant chemotherapy, nor have enough study data been compiled to compare craniospinal irradiation with the intra-CSF administration of chemotherapy.

Regarding the management of recurrent ependymomas, consensus exists on the extent of the disease evaluation. In the recurrent setting, evaluation should include contrast-enhanced neuraxis MRI and CSF cytology for all patients. When disseminated disease is demonstrated, the treatment is altered. In one study of 36 patients with recurrent intracranial ependymoma by Goldwein et al, 12 received conventional radiotherapy, 33 underwent repeat surgery, and all received chemotherapy. They reported that the median time to recurrence was nearly 3 years. When relapse occurred (which happened in the majority of the study population), 78% of cases were determined to be local and 14% were considered to be local with concomitant distant metastasis. Most patients experienced repeat relapse (79%); of those, 80% were determined to have had a local component to the relapse. Two-year PFS and overall survival rates were low at 23% and 29%, respectively. Median PFS was 12 months, and the median duration of response in patients with stable or responsive disease was 9 months. Based on these results, Goldwein et
al proposed the intra-CSF administration of chemotherapy to patients with metastatic ependymoma who had not received craniospinal irradiation.

**Primitive Neuroectodermal Tumor**

Primitive neuroectodermal tumors (PNETs) are made up of undifferentiated (medulloblastoma) and differentiated tumors (cerebral neuroblastoma, olfactory neuroblastoma, pineoblastoma, retinoblastoma). Because PNETs, specifically medulloblastoma, are associated with CSF dissemination, standard initial care for patients with PNETs includes craniospinal irradiation regardless of the extent of disease. Currently, there is no role for intra-CSF administration of chemotherapy in patients with CSF-disseminated PNET. Furthermore, no adjuvant studies have suggested that craniospinal irradiation should be provided in combination with the intra-CSF administration of chemotherapy in patients with M+ disease. However, administration of intra-CSF chemotherapy may allow for further dose reductions of craniospinal irradiation, according to some authors. In addition, the intra-CSF administration of chemotherapy can be considered in patients with positive findings on CSF cytology after receiving craniospinal irradiation, although the rate of this occurrence is not defined. By contrast, the results of several studies have shown that M1 disease defined as positive findings on CSF cytology in metastatic microscopic disease alone does not correlate with reduced rates of survival, suggesting a very limited role for intra-CSF administration of chemotherapy in the initial management of medulloblastoma. Among children with medulloblastoma who had an average-level risk, data suggest that reducing the craniospinal irradiation dose in conjunction with systemic chemotherapy can result in an excellent 5-year event-free survival rate of 79% and without an increased risk of neuroaxis failure.

Anaplastic/large cell medulloblastoma is characterized by frequent CSF dissemination, and the disease often manifests in an aggressive way. A report by Leonard et al evaluated the genetic and clinicopathological features of 7 patients with anaplastic/large cell medulloblastoma at their institution. Metastasis to the lymph nodes was observed in 1 case, isochromosome 17q was discovered in 5 cases, and CSF dissemination was discovered in all 7 cases. Aneuploidy, which was defined as evidence of chromosomal gains or losses, was present in 3 of the tumors studied, and MYC amplification was observed in 3. The authors concluded that, based on their findings, the morphological characteristics of this type of medulloblastoma suggest a more advanced stage of tumor than that found in the classical presentation of medulloblastoma.

Because tumor dissemination frequently occurs along CSF pathways, MRI after surgery is routinely performed to stage medulloblastoma. Meyers et al retrospectively reviewed the records of 112 patients with medulloblastoma who underwent surgical resection. The rate of sensitivity for spine MRI was 83% for its ability to detect disseminated tumor; by contrast, the rate of sensitivity of contemporaneous CSF cytology was 60%. When multiple samples were subsequently obtained, the sensitivity rate increased to 78% for CSF cytology analysis. However, compared with CSF cytology analysis, spine MRI still had a higher overall rate of diagnostic accuracy for detecting early disseminated medulloblastoma. If both CSF analysis and spine MRI were performed less than 2 weeks preoperatively, then false-positive results were more likely to occur. The researchers also reported that CSF cytology findings were, at times, positive for disseminated tumor even in cases in which negative results on spine MRI were found. Thus, a delay of more than 2 weeks following surgery could reduce the likelihood of false positives.

One group of researchers concluded that death caused by medulloblastoma is mainly associated with the recurrence of leptomeningeal dissemination. Yang et al studied the miRNA-expression profiles of 29 cases of medulloblastomas as to whether CSF seeding was present. They discovered reduced levels of expression of miR-192, a microRNA precursor, in the CSF-seeding group. Their findings suggested that, by modulating cell proliferation and anchoring ability, miR-192 expression could suppress the leptomeningeal dissemination of medulloblastoma.

To study whether metastasis influences prognosis, Miralbell et al retrospectively reviewed data from 86 children with medulloblastoma. For M0, Mx, M1, and M2/3 disease, they found that the 5- and 10-year rates of overall survival were 76% and 54%, 68% and 50%, 36% and 25%, and 22% and 22%, respectively. Among patients with M1 and M2/3 disease, the researchers did not observe any significant differences in survival. Seven of the 26 patients had positive findings on CSF cytology performed postoperatively. Outcomes were reportedly similar among the 6 patients with stage M1 disease and significantly different from those with M0 disease. Nineteen of the studied patients had M2/3 disease, and of these, 8 had positive findings on CSF cytology, 5 had negative findings on CSF cytology, and 6 had findings that were unknown. A positive finding on CSF cytology, either before or after surgery, predicted poor outcomes, although the researchers noted that postoperative cytology findings were more likely to be concordant with CSF analysis performed prior to surgery and appeared to be reflective of similar prognostic significance.

Perioperative neuraxis MRI and intracranial/lumbar CSF cytology can be used in a complementary manner to help decrease the rates of dissemination that go diagnostically undetected. Terterov et al studied...
Germ Cell Tumor

Germ cell tumors make up less than 1% of all primary brain tumors; germ cell tumors have a male predominance (~ 75%) and up to 70% of cases occur in the first 2 decades of life. Similar to ependymoma and PCNSL, germ cell tumors have a proclivity for CSF dissemination. Thus, staging of the disease, which includes CSF cytology, oncofetal protein analysis, and contrast-enhanced neuraxis MRI, should be performed at the time of diagnosis. When the patient is first diagnosed, they often have metastatic disease occurs in 35% of nonseminomatous germ cell tumors, with a predominance for bone. One exception is isolated CSF dissemination, which is defined as a positive finding on CSF cytology or the presence of subarachnoid nodules (intracranial or spinal) on neuroradiography, occurs in one-half of patients with recurrent medulloblastoma. In general, however, disseminated, recurrent medulloblastoma is managed with systemic chemotherapy regardless of CSF spread of disease. One exception is isolated CSF dissemination and medulloblastoma managed with the intra-CSF administration of chemotherapy. Exactly how to extrapolate information from the limited available data on the intra-CSF administration of chemotherapy for the treatment of PNET is unclear, and all recommendations for treatment should be considered in this context.

C-kit expression in CSF and its clinical significance in germ cell tumors was examined by Miyahara et al. C-kit was diffusely expressed on the cell surface of the germinoma cells in all 18 specimens that contained germinomas. Only some mature components had immunoreactivity to c-kit in the immature teratoma specimens. Negative findings were seen in syncytiotrophoblastic giant cells, a finding that suggested germinoma cells primarily express c-kit. The researchers also used a sandwich enzyme-linked immunosorbent assay to analyze 47 CSF samples obtained from 32 germ cell tumors, and they found that the level of s-kit was significantly higher in samples that included syncytiotrophoblastic giant-cell germinomas compared with control samples or samples that contained teratomas or non–germ-cell brain tumors. Miyahara et al also found that s-kit concentrations were much higher in the pretreatment samples compared with the samples retrieved at the time of tumor recurrence and those retrieved during tumor remission. S-kit concentration in the CSF was associated with the clinical course of the disease. These results in-
dicate that the level of s-kit concentration in CSF could be used as a clinical marker in germinomas to detect possible recurrence.\textsuperscript{166}

**Treatment**

Lack of standardized diagnostic methods, difficulties determining treatment response, and lack of large, randomized controlled trials complicate the evaluation and management of neoplastic meningitis.\textsuperscript{167-178} Those issues notwithstanding, evidence suggests that palliative therapies for neoplastic meningitis are effective and, in certain patients, can prolong survival. Typically, treatment is multimodal and involves a combination of surgery, radiotherapy, and chemotherapy. The Figure outlines a treatment algorithm for neoplastic meningitis.\textsuperscript{167-178}

In general, the only neurological manifestations of neoplastic meningitis that improve with treatment are related to pain. Neurological signs and symptoms (eg, ataxia, confusion, cranial nerve deficits, segmental weakness) only stabilize or minimally improve following treatment.\textsuperscript{179-190}

**Surgery**

Surgery is utilized to place a ventriculoperitoneal shunt in cases of symptomatic hydrocephalus and an intraventricular catheter and subgaleal reservoir are placed for the administration of cytotoxic agents.\textsuperscript{191-198} Access to the subarachnoid space by lumbar puncture or via an intraventricular reservoir system can be used for the administration of medications. The intraventricular reservoir system is the preferred approach because it is more comfortable for the patient, is safer than repeat lumbar puncture, is simpler to perform, and it results in a more uniform distribution of the cytotoxic agent into the CSF space, thus producing more consistent CSF levels.\textsuperscript{191-198} In up to 10% of lumbar punctures, drug delivery occurs in the epidural space, even if CSF re-
Communicating hydrocephalus, a condition associated with increased intracranial pressure, can be caused by neoplastic meningitis. Whole-brain radiotherapy may alleviate elevated intracranial pressure presumably by relief from obstructed sites of CSF flow, thereby obviating the need for CSF shunting. Alternatively, if hydrocephalus is present, then placing a ventriculoperitoneal shunt often relieves intracranial hypertension with attendant clinical improvement. If available, the use of an inline, on/off valve and reservoir to aid in the intra-CSF administration of chemotherapy can be installed in parallel with the ventriculoperitoneal shunt. Importantly, however, not all patients can tolerate the shunt being turned off to allow for the intra-CSF-administered drug to circulate.\(^{191-198}\)

In persistent cases of ventricular CSF blockage, a lumbar catheter and reservoir, as well as a ventricular catheter, may be used to provide intrathecal chemotherapy to the spine. However, persistent cases of CSF flow blocks following radiotherapy may be more appropriately managed with supportive care only. On occasion, meningeal biopsy may be required to confirm neoplastic meningitis on pathology; however, these biopsies are rarely performed today because, in general, leptomeningeal abnormalities can be determined by MRI, an abnormal CSF profile, or clinical examination findings consistent with neoplastic meningitis.\(^{191-198}\)

### Radiotherapy

Radiotherapy is used in cases of neoplastic meningitis as a means to correct abnormal CSF flow (demonstrable on radionuclide ventriculography), to relieve disease-related symptoms (eg, cauda equina syndrome), and to decrease the radiographic-identified bulky disease (eg, co-existent parenchymal brain metastases). Even without evidence on radiography of bulky disease, patients with a symptomatic site of disease may benefit from radiotherapy. As an example, radiotherapy to the lumbosacral spine in patients who experience symptoms of cauda equina syndrome (back pain and lower-extremity weakness and sensory disturbance) is often employed and improves associated pain and halts the imminent progression of symptoms. Similarly, whole-brain or skull-base radiotherapy is often administered to patients with cranial neuropathies.\(^{199-210}\)

Radiotherapy is indicated for patients with bulky radiographic disease because the intra-CSF administration of chemotherapy is limited by diffusion to 2 to 3 mm of penetration into the tumor nodules. In addition, involved-field radiotherapy should be employed to correct abnormalities in CSF flow because normalizing CSF flow obstruction is associated with improvements in patient outcomes.\(^{199-210}\) Rarely is whole-neuraxis radiotherapy used to treat neoplastic meningitis from solid tumors because of its association with significant levels of systemic toxicity (eg, severe myelosuppression, mucositis) and because it is not curative.\(^{199-210}\)

### Chemotherapy

Among all of the therapies used to manage neoplastic meningitis, chemotherapy is the single treatment modality used to treat the whole neuraxis, administered either intrathecally or systemically.\(^{199-210}\) In patients with solid tumors, the intra-CSF administration of chemotherapy is the mainstay of neoplastic meningitis management, and several groups suggest that administering chemotherapy to the CSF improves outcomes in these patients.\(^{211-220}\)

However, most studies exclude patients who are too ill to receive any treatment — a number that could approach one-third of patients with neoplastic meningitis.\(^{211-220}\)

Cytarabine and its liposome formulation, methotrexate, and thiotepa are typical chemotherapeutic agents used in the management of neoplastic meningitis. In randomized trials of adult patients with neoplastic meningitis and solid tumors, no response differences were reported between comparisons of single-agent methotrexate and thiotepa or between multiple agents (methotrexate/thiotepa/cytarabine or methotrexate/cytarabine and single-agent methotrexate).\(^{211-220}\) The Table outlines common regimens for these drugs. Intra-CSF, sustained-release cytarabine liposome administration has been shown to result in cytotoxic cytarabine levels in the CSF for at least 10 days.\(^{49-52,55,56,162,163,168,169}\) When comparing patients with neoplastic meningitis and solid tumors receiving bimonthly cytarabine liposome injection and in those receiving biweekly methotrexate, the cytarabine regimen was shown to result in a longer time to neurological progression and better quality of life.\(^{49-52,55,56,162,163,168,169}\) These findings were later confirmed in studies of lymphomatous meningitis, suggesting that the injection formulation of cytarabine should be considered first-line treatment for neoplastic meningitis when investigational agents are not available.\(^{49-52,55,56,162,163,168,169}\)

The intra-CSF administration of chemotherapy is based on the suggestion that, when these same drugs are systemically administered, all have poor penetration into the CSF. As a consequence, therapeutic levels in the CSF are generally not achieved. Exceptions are systemic high-dose methotrexate, thiotepa, and cytarabine, all of which can result in cytotoxic levels in the CSF.\(^{211-220}\) However, systemic administration of these agents is limited by the challenge of incorporating them with other chemotherapy regimens being used to manage the primary disease and their associated systemic toxicity. Several groups suggest that intra-CSF chemotherapy does not improve treatment outcomes, because systemic therapy can reach the subarachnoid deposits through their vascular supply.\(^{211-220}\)
Bokstein et al\textsuperscript{164} published a retrospective comparison of patients who received systemic chemotherapy and radiotherapy to involved areas in combination with or without intrathecal chemotherapy. Between the 2 groups of patients, no significant differences in rates of median survival, response, and long-term survival were observed. Glantz et al\textsuperscript{167} published the data from 16 patients who were treated with intravenous, high-dose methotrexate. Outcomes were compared with a control group (n = 15) who received intra-CSF administration of methotrexate. Rates of survival and response were significantly higher in the group receiving methotrexate via the intravenous route of administration.\textsuperscript{167} Another report was published on 2 patients with breast cancer who were receiving systemic hormonal therapy to manage their neoplastic meningitis,\textsuperscript{168} and findings from anecdotal reports have suggested that systemic chemotherapy is effective for managing meningeal gliomatosis.\textsuperscript{211-220}

Nonetheless, intra-CSF administration is still the preferred route of administration for chemotherapy to manage neoplastic meningitis. Other agents, such as diaziquone, gemcitabine, interferon \(\alpha\), mafosfamide, temozolomide, and topotecan, have been evaluated in an attempt to improve therapeutic efficacy.\textsuperscript{179-190} Immunotherapy utilizing interleukin 2 and interferon \(\alpha\), gene therapy, and iodine 1\textsuperscript{31}-radiolabeled monoclonal antibodies are among several other therapeutic options being explored in clinical trials.\textsuperscript{179-190}

### Supportive Care

Aggressive treatment is not appropriate for every patient with neoplastic meningitis. Therapy using a multimodal approach should be offered to patients with a Karnofsky performance status score higher than 60 (ie, independent in activities of daily living) and for those whose life expectancy will be more than 3 months. Supportive care should be offered to every patient, regardless of whether disease-directed therapy is provided. Such options, if necessary, can include antidepressants, anxiolytics, opioids for adequate analgesia, and anticonvulsants for seizure control (incidence rate of 10\%-15\% in patients with neoplastic meningitis). Although corticosteroids have a limited role in the management of neurological symptoms related to neoplastic meningitis, they may be useful for control of nausea/vomiting (along with added routine antiemetics) and the management of vasogenic edema associated with epidural or intraparenchymal metastases. Psychostimulants may also have a role in the management of decreased attention and for the treatment of somnolence secondary to whole-brain radiotherapy.\textsuperscript{179-190}

### Conclusions

Neoplastic meningitis is a difficult disease to treat. Most reports of neoplastic meningitis treat all tumors as a single histology notwithstanding differences with respect to options for treatment and expected outcomes. Because clinical trials in oncology use specific

<table>
<thead>
<tr>
<th>Drug</th>
<th>Induction</th>
<th>Consolidation</th>
<th>Maintenance</th>
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<tbody>
<tr>
<td></td>
<td>Bolus</td>
<td>Concentration</td>
<td>Bolus</td>
</tr>
<tr>
<td></td>
<td>( \times ) Time</td>
<td>( \times ) Time</td>
<td>( \times ) Time</td>
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<tr>
<td>Cytarabine</td>
<td>25–100 mg BIW or TIW ( \times 4 ) wk</td>
<td>25 mg/d for TIW ( \times 4 ) wk</td>
<td>25–100 mg QW ( \times 4 ) wk</td>
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<tr>
<td>Cytarabine liposome injection</td>
<td>50 mg Q2W ( \times 8 ) wk</td>
<td>—</td>
<td>50 mg Q4W ( \times 24 ) wk</td>
</tr>
<tr>
<td>Etoposide</td>
<td>0.5 mg BIW ( \times 6 ) wk</td>
<td>—</td>
<td>0.5 mg QW ( \times 6 ) wk</td>
</tr>
<tr>
<td>Interferon (\alpha)</td>
<td>1 ( \times 10^6) U TIW ( \times 4 ) wk</td>
<td>—</td>
<td>1 ( \times 10^6) U TIW EOW ( \times 4 ) wk</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>10–15 mg BIW ( \times 4 ) wk</td>
<td>2 mg/d ( \times 5 ) d EOW ( \times 8 ) wk</td>
<td>10–15 mg QW ( \times 4 ) wk</td>
</tr>
<tr>
<td>Rituximab</td>
<td>25–40 mg QW or BIW ( \times 4 ) wk</td>
<td>—</td>
<td>25–40 mg QW or EOW ( \times 4 ) wk</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>10 mg BIW or TIW ( \times 4 ) wk</td>
<td>10 mg/d TIW ( \times 4 ) wk</td>
<td>10 mg QW ( \times 4 ) wk</td>
</tr>
<tr>
<td>Topotecan</td>
<td>400 mg BIW ( \times 6 ) wk</td>
<td>—</td>
<td>400 mg QW ( \times 6 ) wk</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>150 mg QW ( \times 4 ) wk</td>
<td>—</td>
<td>EOW ( \times 4 ) wk (2 doses total)</td>
</tr>
</tbody>
</table>

BIW = twice weekly, EOW = every other week, QM = once monthly, Q2W = every 2 weeks, Q4W = every 4 weeks, QW = once weekly, TIW = thrice weekly.
tumor histology, comparing treatment responses of carcinomatous meningitis due to gliomas with primary central nervous system (CNS) lymphoma may be misleading. Consensus opinion suggests that lymphomatous meningitis is more sensitive to chemotherapy than cerebrospinal fluid (CSF)–disseminated meningioma or meningeal gliomatosis, so rates of survival between these patient populations will likely be different.

Treatment of neoplastic meningitis is complicated because determining who should receive aggressive, CNS-directed therapy is difficult. Not all patients are candidates for aggressive therapy directed at the CNS, but few guidelines exist as to the most appropriate therapeutic options available. Palliation may be appropriate for patients with neoplastic meningitis who would not be considered appropriate candidates for an aggressive approach.179–190 Oftentimes, therapy directed at palliation may improve quality of life by protecting patients from experiencing treatment-related toxicity.

Further adding to the complexity of the disease, optimal therapy for neoplastic meningitis is poorly defined. Given these constraints, therapy for neoplastic meningitis is palliative in nature. Rarely, treatment may have a curative intent. Based on data extrapolated from several prospective, randomized trials of primary brain tumors, the median rate of survival for neoplastic meningitis is only several months.

In general, the therapeutic response of neoplastic meningitis is a function of clinical response and, secondarily, of CSF cytology. No CSF parameters have been shown to predict rate of response, except for CSF cytology and, in limited instances, CSF biochemical markers. CSF cytology may manifest a rostrocaudal dissociation; thus, consecutive negative findings require that lumbar and ventricular cytological testing be performed in a clinical trial to confirm response.

References


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