Leptomeningeal Metastases: Current Concepts and Management Guidelines

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Abstract
Neoplastic infiltration of the meninges occurs when malignant cells gain entry into the cerebrospinal fluid (CSF). This is clinically recognized in 4% to 7% of all cancer patients. Leptomeningeal metastases may involve any part of the neural axis via tumor seeding; thus, a multitude of clinical presentations involving one or more domains exist, including the cerebral hemisphere, cranial nerves, and spinal cord and roots. The diagnosis of CSF metastases is often delayed and not appreciated until fixed neurologic deficits become evident. Adequate cytologic analysis of CSF fluid, neuroradiography of brain and spine, and an appropriate clinical context are the key elements in diagnosing leptomeningeal metastases. A major challenge of treating neoplastic meningitis is the importance of treating the entire neural axis and stratifying patients in poor risk or good risk categories. Treatment is palliative and involves stabilizing neurologic status and prolonging survival. Median survival for untreated patients is 4 to 6 weeks. Treatment in a broad perspective entails radiotherapy and chemotherapy (systemic and intra-CSF). Commonly used intra-CSF chemotherapy regimens use drugs such as methotrexate, cytarabine, thiopeta, and a sustained-release liposome-encapsulated form of cytarabine (Depocyt, SkyePharma, London, UK). Patients with neoplastic meningitis usually experience a limited survival, even when treated using close adherence to evaluation algorithms and treatment protocols. In randomized controlled clinical trials using currently available intra-CSF chemotherapeutic agents, median survival in carefully selected, study-eligible groups of patients was 2 to 6 months. (JNCCN 2005;3:693–703)

Neoplastic infiltration of the leptomeninges occurs when malignant cells gain entry into the cerebrospinal fluid (CSF). Although this is recognized clinically in approximately 4% to 7% of all cancer patients,1–4 asymptomatic involvement of the leptomeninges is far more common, as determined on postmortem reports.1–4 The frequency of leptomeningeal disease in autopsy series averages 20% and is much higher in certain diseases.2,5 The most common solid tumors associated with meningeal dissemination are breast cancer (particularly the infiltrating lobular subtype), lung tumors (particularly relapsed small cell lung cancer), melanoma, and cancer of the gastrointestinal system.2,6–13 Leptomeningeal metastases from solid tumors confer a poor overall prognosis. Mean survival from the time of diagnosis is 2 to 4 months. However, a subset of patients, particularly those with lymphoma or breast cancer, may survive for more than 12 months with reasonable quality of life.

Pathophysiology
The brain and spinal cord are covered by the meninges, a three-layer membrane composed of the dura mater, the arachnoid, and the pia mater. The leptomeninges consist of the arachnoid and pia mater, and CSF is contained in the subarachnoid space, which separates these two membranes. In adults, the subarachnoid space normally contains approximately 140 mL of CSF, a volume that does not vary significantly with height or weight. Because approximately 800 mL of CSF is produced over 24 hours, the entire CSF volume is replaced more than 5 times each day.

CSF is produced by the choroid plexus. It flows out the lateral ventricles through the foramina of Monro into the third ventricle, through the aqueduct of Sylvius to the fourth ventricle, then through the foramina of Magendie and Luschka to the base of the brain, where it travels...
caudally to the base of the spine (lumbar sac) and ros-
trally over the cerebral convexities. Because irregular 
trabeculae partition the subarachnoid space through-
out its length and delicate pial blood vessels traverse 
it, tumor cells have abundant opportunity to accumu-
late and obstruct CSF flow at any point along the 
pathway.\textsuperscript{14}

**Tumor Seeding**

Tumor cells can gain access to the CSF in 6 ways: (1) 
hematogenously through penetration of the arach-
noid vessels; (2) via direct invasion through the 
choroid plexus; (3) in a direct extension from sub-
dural, epidural, or intraparenchymal metastases; or 
(4) by tracking along peripheral nerves. In addition, 
(5) rarely, tumors arise directly within the meninges.

Primary CSF lymphoma, primary meningeal melano-
a, and a variety of primary meningeal sarco-
mas (including malignant peripheral nerve sheath 
tumors or “malignant schwannomas”) are the most 
common. Finally, (6) neoplastic meningitis can also 
develop after surgical resection of cerebellar metas-
tases, as a result of inadvertent spillage of malignant 
cells into the CSF.\textsuperscript{15,16} The frequency of this compli-
cation after resection of supratentorial metastases or 
primary brain tumors is uncertain.

Tumor cells within the subarachnoid space may in-
vade the leptomeninges focally, extend along the lep-
tomeninges, spinal or cranial nerves, invade the cortex 
through the Virchow-Robin spaces, or disseminate diffusely throughout the neuraxis via the CSF. 

The most common sites of radiographic and pathologic leptomeningeal tumor involvement are the base of 
the brain (basilar cisterns or posterior fossa) and the base of the spine (cauda equina), probably due to slow 
flow of CSF in these locations.

**Clinical Implications**

Because tumor cells have access to all levels of neu-
raxis, patients with neoplastic meningitis typically 
present with a wide array of signs and symptoms, of-
ten at multiple levels. These may be separated into 
deficits related to cranial nerves, spinal cord and spinal 
nerves, or cerebral hemispheric involvement and those 
secondary to obstruction of CSF flow.\textsuperscript{1,4,6–10,17–19}

Infiltration of cranial and spinal nerves as they 
traverse the CSF can produce multiple cranial nerve 
palsies or radiculopathies, and spinal cord involve-
ment can result in a myelopathy. Invasion or irritation 
of the cortex may be associated with seizures, focal 
neuropathic deficits, or encephalopathy. Tumor cells oc-
cluding pial blood vessel may result in focal deficits 
with a stroke-like onset. Obstruction of CSF flow, with 
or without hydrocephalus, produces symptoms refer-
able to increased intracranial pressure. These include 
headache, nausea, vomiting, neurocognitive deficits, 
encephalopathy, and weakness.

**Diagnosis**

Although the characteristic CSF profile of lep-
tomeningeal metastases includes high opening pres-
sure, low glucose, high protein, and a lymphocytic 
pleocytosis, these findings are inconsistently corre-
lated with the presence or activity of neoplastic menin-
gitis.\textsuperscript{1,4,20,21} Nevertheless, a completely normal lumbar 
CSF examination is uncommon in the setting of 
neoplastic meningitis, occurring in fewer than 10% 
of newly diagnosed cases.

**CSF Cytology**

The diagnostic gold standard for neoplastic meningi-
tis is the cytologic identification of malignant cells 
within the CSF.\textsuperscript{4,22} The specificity of CSF cytology is 
excellent, and false-positive results are rare in the 
hands of experienced cytopathologists. In contrast, 
false-negative results are neither rare nor the result 
of inexperience, and they present a major problem for 
clinicians.\textsuperscript{4,22} Specific guidelines for minimizing false 
negative results include\textsuperscript{22} withdrawing at least 10 to 15 
\text{mL} of CSF for cytologic analysis; immediate process-
ing and good handling of the specimen; obtaining CSF 
from a site of known leptomeningeal disease;\textsuperscript{23,24} and 
repeating the procedure at least once if initial cytol-
ogy is negative.

The optimal number of samples required to min-
imize false-negative results is a matter of debate. In a 
compilation of data from 9 reports including 532 pa-
ients, cytologic positive rates were 71\%, 86\%, 90\%, 
and 98\% for 1, 2, 3, and more than 3 samples per pa-

tient.\textsuperscript{22} However, these series varied according to the 
volume of CSF withdrawn, specimen processing, and 
whether or not intervening treatment had been admin-
istered. In most cases, high yields can be obtained with 
two separate large-volume samplings, with little if any 
benefit gained by subsequent samplings.

Despite these measures, as many as 50% of cases 
will have persistently negative CSF cytology despite 
clinically or radiographically unequivocal disease. In
such cases, the diagnosis can be made by neuroimaging alone or in the context of clinical features consistent with leptomeningeal metastases.²⁴

**CSF Biologic Markers**

Besides cytology, the CSF is a source of biologic markers that may provide information regarding the presence of malignant cells. CSF assay for tumor antigens (e.g., MART-1 and MAGE-3 in melanoma²⁵) and biochemical markers (e.g., carcinoembryonic antigen, alpha fetoprotein [AFP], the beta subunit of human chorionic gonadotropin [beta HCG], beta 2 microglobulin, glucose-6-phosphate isomerase, gastrin releasing peptide, immunoglobulin indices, and oligoclonal bands) may be useful to establish the diagnosis of neoplastic meningitis in cytotologically negative cases, particularly if the CSF concentration is substantially higher than the simultaneous serum concentration.²²–²⁴

Moreover, CSF tumor marker levels may also be useful for assessing the response to therapy. CSF immunohistochemistry may provide diagnostic information, or may permit a refinement in diagnosis in some patients, particularly those without an apparent primary tumor source.³⁵ In patients with suspected lymphomatous meningitis, CSF flow cytometry and molecular analyses such as polymerase chain reaction assays to identify immunoglobulin gene rearrangements (e.g., clonal V-J rearrangements) are more sensitive than routine cytologic analysis. At some institutions, these are a standard diagnostic procedure.³⁶–³⁹ Application of this technique to other tumor types may be feasible, although technical barriers have prevented more widespread use.

Novel biochemical markers implicated in tumor invasion, angiogenesis, and metastasis (e.g., vascular endothelial growth factor, matrix metalloproteinases, and lipid-associated sialic acid) are promising.⁴⁰–⁴² However, a rapid, technically simple, and reliable assay with high sensitivity for neoplastic meningitis and the ability to accurately predict clinical outcome remains elusive.

**Radiographic Studies**

Although gadolinium-enhanced magnetic resonance imaging (MRI) may provide definitive evidence of leptomeningeal metastases,³¹–³⁶ its sensitivity and specificity remain to be established.²⁴ In up to 40% of patients, MRI may show diffuse leptomeningeal contrast enhancement and thickening or nodular deposits in the subarachnoid space, with or without hydrocephalus. In some patients who present with encephalopathy, positron emission tomography (PET) scanning can show diffusely diminished glucose use in an otherwise normal-appearing brain. This situation may be reversible after cranial irradiation.⁴⁷

**Treatment**

The goals of treatment include improvement or stabilization of neurologic status and prolonging survival. In untreated patients, median survival is 2 to 6 weeks, and death generally results from progressive neurologic disease. A major challenge in treating neoplastic meningitis is the necessity of treating the entire neuraxis. If treatment is directed only towards symptomatic areas, disease progression inevitably occurs at untreated sites. The NCCN’s treatment algorithm for neoplastic meningitis stratifies patients into good and poor risk categories for the purpose of treatment planning.⁴⁶

For patients with a poor Karnofsky performance status, multiple, serious, fixed neurologic deficits, and extensive systemic cancer with few therapeutic options, treatment should be geared towards palliation. Focused radiation therapy (RT) designed for symptomatic relief may be appropriate, and analgesics may be administered for persistent pain. Corticosteroids rarely reverse fixed deficits from neoplastic meningitis, but they may improve headache and radicular pain more effectively than analgesics. Anticonvulsants should be reserved for patients with seizures (10% to 20% of cases), and should not be administered prophylactically. Serotonin reuptake inhibitors or stimulant medications (e.g., modafinil or methylphenidate) may benefit patients with significant depression or fatigue.

Palliative therapy should also be considered for the majority of patients with leptomeningeal gliomatosis, because prognosis is poor, even with combined modality therapy.⁴⁷ Patients with good risk include those with a KPS of 60 or above, absence of or modest fixed neurologic deficits, minimal disease burden, or systemic cancer for which there are reasonable treatment options. For these individuals, RT to bulky or symptomatic areas of leptomeningeal disease, intrathecal (IT) therapy to treat low-volume or liquid phase disease, and optimal systemic treatment for the extraneural disease component are appropriate.

**Pretreatment Evaluation**

Before IT treatment, a CSF flow study via a radionuclide cisternogram or by lumbar puncture is imperative.
Abnormal flow is seen in up to one third of patients with neoplastic meningitis, frequently in the absence of hydrocephalus or other abnormalities on conventional neuroimaging studies.17–19 Disturbed CSF flow may occur at the base of the brain (ventricular outlet obstruction), within the spinal canal, or over the cortical convexities. Such abnormalities interfere with the homogeneous distribution of intra-CSF—administered agents and can alter both efficacy and toxicity. RT to the sites of abnormal CSF flow, even in the absence of an MRI abnormality, can reverse the flow abnormality and allow safe administration of intrathecal chemotherapy.

Response Evaluation
Meticulous assessment of the therapeutic benefit is essential to support the continued use of aggressive treatment in the setting of responsive disease. In the setting of nonresponsive disease, it permits the early use of alternative therapy or the institution of palliative care, where appropriate.

CSF Cytology: Cytologic evaluation of the CSF is a critical component of positive response assessment during IT therapy.22,27 CSF should be sampled at each site (lumbar and ventricular) from which malignant cells were identified before treatment, because cytologic differences in ventricular and lumbar fluid are common. Many investigators require 2 successive negative cytologic evaluations from each site before declaring the treatment response, but in clinical practice, the requirement for multiple lumbar punctures (LPs) in patients who have ventricular reservoirs is difficult to meet.

Other Methods: Other methods of response assessment have been suggested, including evaluation of interphase cytogenetics by fluorescence in situ hybridization (FISH),51 and, for patients with lymphoma, serial immunocytochemical or molecular CSF evaluation. These methods may be especially useful for patients with cytologically negative CSF.

Intrathecal Chemotherapy
Intrathecal chemotherapy is the mainstay of therapy for neoplastic meningitis. Currently, 4 chemotherapeutic agents are used for IT treatment: methotrexate (MTX), cytarabine, sustained-release cytarabine (DepoCyt, Skye Pharma, London, UK), and thiopeta. Although MTX is the most frequently used drug for solid tumors, IT cytarabine is more often used for lymphomatous meningitis.

General Principles: IT chemotherapy involves the injection of antitumor agents directly into the CSF either through a subcutaneous reservoir and ventricular catheter (e.g., an Ommaya reservoir), or into the lumbar thecal sac via LP. Intrathecally administered chemotherapy is efficacious for small leptomeningeal deposits and individual tumor cells floating in the liquid phase of the CSF. However, it cannot reliably eradicate bulky disease such as that seen on MRI because of limited diffusion of drug into subarachnoid tumor deposits, along nerve root sleeves, and into the Virchow-Robin spaces.51,52 Nevertheless, an important goal of IT therapy is to forestall progression of disease within the subarachnoid space and the appearance of new neurologic symptoms.

Although IT chemotherapy can be administered directly into the lumbar CSF or into the lateral ventricle, intraventricular administration using a reservoir device has advantages:

1. Frequent administration of chemotherapy via LP is cumbersome and resource intensive for both the patient and the clinician.
2. Intrathecal chemotherapy administration may result in the inadvertent introduction of drug into the epidural or subdural space.53
3. Even in the absence of obstruction to CSF flow, administration of chemotherapy via LP does not guarantee therapeutic drug levels at higher CSF levels.54
4. Drug exposure in the ventricular CSF after an intralumbar dose of chemotherapy is only one tenth of that achieved after an equivalent intraventricular dose. Intraventricular administration also permits more uniform drug distribution throughout the neuraxis.53

Perhaps as a consequence of these issues, a survival benefit has been suggested for intraventricular compared with lumbar administration of IT chemotherapy.51 Whether the magnitude of this advantage is sufficient to outweigh the risk of surgery for reservoir placement and the increased risk of infection is unknown.

Technique: It is critically important that the intrathecally administered IT chemotherapy be administered into the CSF fluid volume not be greater after chemotherapy than before intrathecal administration. Patients with neoplastic meningitis are often precariously poised on the edge of the ventricular compliance (“pressure-volume”) curve, and even if they are relatively asymptomatic, symptoms (headache, nausea and vomiting, obtundation, herniation) may develop precipitously if
even small amounts of additional fluid are added to the total volume. If the chemotherapy agent is diluted in a substantial (7 to 10 mL) volume of diluent, CSF for laboratory studies, fluid for flushing the chemotherapy syringe, and additional fluid to account for the volume of administered chemotherapy all must be removed before chemotherapy instillation (isovolumetric administration).

**Methotrexate:** Methotrexate is the most frequently used drug for IT chemotherapy. The usual dose of IT MTX is 10 to 15 mg, generally administered twice weekly for 8 treatments, followed by weekly administration for 4 treatments, and finally by monthly treatment. As with all chemotherapeutic agents given intrathecally to adults, no dosage adjustment is made based on weight or body surface area. Therapeutic concentrations of MTX (≥1 μmol/L) can persist within the CSF for 48 hours after each dose.

Accidental overdoses of MTX can be treated with carboxypeptidase G2. Intrathecal MTX is not metabolized by the CNS but instead reabsorbed by the choroid plexus into the systemic circulation. A continuous low systemic concentration of MTX may lead to myelosuppression, particularly in patients with poor bone marrow reserve, renal insufficiency, third space fluid collections (e.g., large pleural effusions, ascites), or abnormal CSF flow. Oral leucovorin (folinic acid, 10 mg) may be administered twice daily, beginning on the day of treatment and continuing for 3 days, to mitigate systemic toxicity. Leucovorin does not appear to cross the blood-brain barrier in amounts sufficient to interfere with the effect of MTX in the CSF. Leukoencephalopathy may also occur, particularly in patients with abnormal CSF flow or in patients who are receiving concurrent CNS radiation.

Relative contraindications to IT MTX include renal insufficiency, large pleural effusions, ascites, and abnormal CSF flow. Because MTX is partially bound to serum albumin, toxicity can be increased because of displacement when certain drugs are co-administered (aspirin, phenytoin, sulfonamides, and tetracycline).

Intrathecal MTX successfully clears malignant cells from the CSF in 20% of cases. The optimum duration of therapy in responding patients is uncertain; however, treatment beyond 6 months in such patients may be unnecessary. An alternative to IT MTX is the systemic administration of high-dose intravenous MTX, at doses that provide therapeutic CSF levels.

**Thiotepa:** Thiotepa is administered intrathecally in 10-mg doses in 2 to 3 doses weekly and then monthly on a schedule similar to MTX. Although thiotepa has a half-life within the CSF of only a few minutes and may be more myelosuppressive than MTX, it has a wide spectrum of activity against many solid tumors. Complete cytologic clearance is achieved in about one quarter of treated patients. In one report, efficacy was similar to MTX, and treatment-related neurotoxicity was slightly less. Thiotepa may be considered for patients for whom prior MTX failed, those with MTX-induced leukoencephalopathy, or those for whom concurrent radiation therapy is unavoidable.

**Cytarabine:** Cytarabine is usually administered intrathecally at a dose of 30 to 100 mg twice weekly, followed by weekly, and then monthly dosing in patients with responding disease. Its half-life within the CSF is 2 to 4 hours, and cytotoxic concentrations are maintained for 24 hours after each dose. Conventional cytarabine is less effective than MTX and thiotepa for most patients with neoplastic meningitis from solid tumors and is usually reserved for patients with either leukemic or lymphomatous involvement. Oral dexamethasone (4 mg twice a day for 5 days) is often added for its lympholytic effect.

A sustained-release liposome encapsulated form of cytarabine (DepoCyt) has been approved for the treatment of patients with lymphomatous meningitis. A major advantage of this preparation is its long half-life within the CSF (141 hours), which permits a reduced dosing frequency (initially once every 2 weeks, followed by once monthly) and increases the likelihood of achieving cytotoxic drug levels within the ventricles with intralumbar instillation. Oral dexamethasone (4 mg twice a day for 5 days) should be used whenever DepoCyt is administered because of the high incidence of chemical meningitis when this drug is administered without oral steroids.

Use of DepoCyt in children between the ages of 3 and 21 is under investigation. A phase I study has suggested a dose of 35 mg every 2 weeks during induction, every 4 weeks during consolidation and every eight weeks during maintenance therapy. Dexamethasone (0.15 mg/kg/dose, twice a day for 5 days) is required with each dose.

DepoCyt appears to be superior to conventional IT cytarabine for treatment of lymphomatous meningitis. In one trial, 28 patients with lymphomatous
meningitis were randomly assigned to DepoCyt or free cytarabine.65 DepoCyt was associated with a significantly higher rate of complete tumor clearance (71% vs. 15%); a significantly longer time to neurologic progression (79 vs. 42 days), and longer survival (100 vs. 63 days). DepoCyt has also shown modest activity in some patients with solid tumor neoplastic meningitis.66

In one trial, in 12 of 43 women (28%) with meningeval involvement from breast cancer, the CSF was cleared of malignant cells.66 This is an efficacy rate similar to other IT-administered agents but requiring fewer IT injections. Low grade headache (90% grade 1 or 2) occurred in 1% of cycles, and low grade arachnoiditis (nausea, vomiting, headache, fever, back pain, meningismus) occurred in 19%.

In a second report, DepoCyt was compared with standard IT MTX in 61 patients with solid tumor-related neoplastic meningitis.66 Although the rate of complete cytologic clearing was not significantly different (26% vs. 20% for DepoCyt and MTX, respectively), the median time to neurologic progression was significantly longer in the DepoCyt group (58 vs. 30 days). In a later report using a Q-TwiST analysis (quality-adjusted time without symptoms or toxicity), the average patient receiving DepoCyt achieved 71 more days of neurologic progression-free survival and 52 more days of overall survival within a 12 month period, at the cost of 7 more days with toxicity.66

**Combination Therapy**

In patients with solid tumor neoplastic meningitis, at least one randomized trial failed to show benefit for combined MTX/cytarabine compared with MTX alone.21 Response rates for combined therapy were not significantly higher (45% vs. 61%) and median survival for the entire group was 8 weeks. Although a preliminary report of a second nonrandomized comparison of MTX alone versus MTX/cytarabine concluded that combined therapy was superior (cytologic response rate, 38.5% vs. 13.8%); the response rate for single-agent therapy was much lower than that reported in the randomized trial.66 Thus, the superiority of combined therapy has not been proven in this setting.

In contrast, combinations of IT MTX and cytarabine are frequently used in patients receiving CNS prophylaxis for lymphomatous or leukemic meningitis.69-71 In one report, coadministration of MTX and cytarabine resulted in complete remission of 14 of 15 patients with recurrent meningeal leukemia or lymphoma.69

**Systemic Chemotherapy**

Systemic chemotherapy offers several potential advantages over IT therapy in patients with neoplastic meningitis.13 The risk of surgery for placement of a ventricular reservoir and of reservoir-associated complications are obviated. Furthermore, patients with an obstruction to normal CSF flow can be treated without correction of the flow abnormality and a wider array of cytotoxic agents can be administered orally or intravenously than is available for IT dosing. This method of delivery may provide a more uniform distribution of drug and because drug is delivered both into the CSF and to leptomeningeal tumor deposits through their systemic vascular supply, bulky disease may also respond to treatment.

**High-Dose Methotrexate:** Most studies of systemic therapy for patients with neoplastic meningitis have focused on agents that are lipid-soluble or that can be given safely at high doses. One example is high-dose intravenous MTX (doses 3 to 8 g/m²), which must be given with intense hydration and leucovorin rescue. In one report, results in 16 patients with solid tumor neoplastic meningitis who received IV MTX (8 g/m²) were compared with those in a control group treated intrathecally.53 Prolonged cytotoxic serum and CSF MTX concentrations, at least comparable to those achieved with IT therapy, were noted, and cytologic clearing of tumor cells occurred in 81% of study patients compared with 60% of historical controls treated intrathecally.55 Others have achieved therapeutic CSF MTX levels with lower doses (700 mg/m2 initially, followed by a 23-hour infusion of 2,800 mg/m²), but without an objective antitumor response.72

High-dose MTX may be repeated every 2 weeks for 2 treatments followed by monthly administration. Disadvantages of this approach include cost and the need for hospitalization for hydration, urinary alkalinization, and leucovorin rescue. If, despite these measures, plasma MTX levels remain high for a prolonged period of time, treatment with carboxypeptidase G2 should be considered. This agent is available from the National Institutes of Health on a compassionate-use basis.

If prolonged high levels of MTX are seen but additional cycles of high-dose MTX are clinically necessary, methylene-tetrahydrofolate reductase (MTHFR) genotyping is recommended to identify
individuals with diminished MTHFR activity who are at increased risk of MTX toxicity. Appropriate intervention, such as reduced doses or the use of carboplatin, can be planned for subsequent cycles. Routine prospective MTHFR genotyping is not recommended.

Cytarabine: The CSF penetration of cytarabine is approximately 20%. Several administration approaches can achieve cytotoxic CSF cytarabine concentrations, including 3 g/m² administered every 12 hours, and 72-hour continuous intravenous infusion of doses more than 4 g/m². However, high-dose systemic administration is associated with significant toxicity, including severe myelosuppression, cerebellar toxicity, encephalopathy, nausea, vomiting, and mucositis.

Further study is warranted to delineate the role of other systemic chemotherapeutic agents (e.g., capecitabine, an orally active 5-fluorouracil prodrug) for the treatment of neoplastic meningitis. An encouraging report of 2 women with leptomeningeal dissemination from breast cancer reported clinical, radiographic, and cytologic improvement with systemic administration of capecitabine and docetaxel.

Radiation Therapy
Radiation therapy (RT) provides more rapid relief of symptoms than does chemotherapy. As a result, standard treatment for neoplastic meningitis has evolved to include palliative RT (30 to 36 Gy in 10 to 12 daily fractions) to sites of symptomatic or bulky disease. In addition, RT to sites of CSF flow block, as shown by radionuclide flow study, may also be necessary before the administration of IT therapy.

Because of the potential for prolonged myelosuppression (see subsequent sections), focal rather than craniospinal irradiation is usually chosen in a number of circumstances, such as for patients with isolated cranial neuropathies (skull-based or whole brain radiotherapy) and those with signs or symptoms of noncommunicating hydrocephalus in whom whole brain radiotherapy is appropriate. Shunting of CSF should be performed in patients with symptomatic or communicating hydrocephalus that does not clear rapidly with treatment. Patients with spinal cord dysfunction (such as lower extremity weakness) are treated with involved-field radiotherapy. Finally, patients with CSF flow obstruction shown by radioisotope ventriculography are treated with involved-field radiotherapy to the site of CSF obstruction.

The major adverse effects of RT are myelosuppression, mucositis, esophagitis, and leukoencephalopathy. Leukoencephalopathy may be especially prominent when RT is administered before or concurrently with IT or systemic chemotherapy, particularly MTX.

Emerging Therapies
Additional (but inadequately studied) agents available for intrathecal (IT) administration include immunotherapeutic approaches with interleukin-2 and interferon-alpha (IFNα), rituximab, and intrathecal RT using radioactive nuclides or radiolabeled monoclonal antibodies as an alternative method of delivering RT. Newer therapies such as IT mafosfamide and etoposide have also been used with beneficial results.

Interferon: Intrathecal IFNα appears to be a promising agent, particularly for lymphomatous meningitis. In one report, IFNα (1 million units per dose) was administered in an aggressive treatment protocol (3 doses weekly for 12 doses, then 3 doses weekly every other week for 6 doses, then 3 doses monthly for 3 doses) to 22 patients with relapsed neoplastic meningitis, 4 of whom had lymphomatous meningitis. Ten (45%) patients, including all 4 with lymphomatous meningitis, showed cytologically complete responses and stable or improved neurologic examinations. Eight of the 10 patients completed all 3 phases of treatment.

One limitation of IT IFNα is its toxicity profile. In the previously discussed study, profound treatment-related fatigue developed in 20 of 22 patients; and fatigue was severe in 10. Sixteen of 22 patients had chemical meningitis. As a result, performance status declined during treatment. In addition, severe encephalopathy developed in a significant number of patients within several days of beginning IT IFNα treatment. This adverse effect is dose dependent and tends to be worse in patients who have received cranial irradiation.

Monoclonal Antibody Therapy: Treatment with intravenous rituximab, a chimeric monoclonal antibody directed against the CD20 surface antigen of B cell lymphocytes, is effective for relapsed non-Hodgkin’s lymphomas. In at least one report, intraventricular rituximab (10–45 mg) successfully cleared malignant cells from the CSF in patients with primary central nervous system lymphoma (PCNSL).

Treatment was associated with substantial CSF antibody levels (up to 10 μg/mL), and mild reversible adverse effects (e.g., nausea, hypotension, and chills).
No antitumor effect was seen on parenchymal lymphoma. Radiolabeled monoclonal antibody therapy is under investigation for patients with both solid tumor and lymphomatous meningitis and may represent an alternative to external beam radiation. 

**Other Agents:** Agents under investigation include dacarbazine, nitrosoureas, busulphan, trimetrexate, melphalan, topotecan, immunotherapy with lymphokine-activated killer cells and interleukin-2, and gene therapy. IT IL-2 has been predominantly studied in patients with leptomeningeal disease from disseminated melanoma. In one preliminary report, 12 of 46 patients showed a response to IT IL-2 (1.2 million units daily for 5 days, then 2 to 3 times weekly as tolerated), with 2 still alive beyond 32 and 90 months, respectively. Significant toxicities included fever, chills, and elevated ICP, which was relieved by frequent Ommaya taps.

**Prognosis**

Despite close adherence to evaluation algorithms and treatment protocols, patients with neoplastic meningitis usually have limited survival. In 4 randomized controlled clinical trials using currently available IT chemotherapeutic agents, median survival in carefully selected, study-eligible groups of patients was 3 to 4 months. Among the reasons for the generally poor outcome are delayed diagnosis of leptomeningeal involvement, irreversible neurologic deficits at the time of diagnosis, and progressive extraneural disease.

Histology, performance status, and disease burden influence treatment outcome. The best median survival is 6 to 7 months for women with breast cancer who are treated aggressively. Other histologic types, particularly leptomeningeal gliomatosis (diffuse meningeal dissemination of a primary intracerebral malignant astrocytoma) do poorly; median survival is approximately 3 months, even with aggressive treatment. Patients with secondary meningeal gliomatosis from low-grade astrocytomas appear to have a longer natural history and may benefit from chemotherapy.

Prognosis is somewhat better for good prognosis subsets (young age, good Karnofsky performance status [KPS], long duration of pretreatment symptoms, well controlled extraneural disease, lymphoma histology) compared with those with adverse prognostic factors (e.g., advanced age, poor KPS, rapidly progressive neurologic or cognitive deficits, bulky subarachnoid disease on neuroimaging studies). Sustained tumor control is reported in a small subset of these patients, encouraging the use of aggressive treatment for patients with good performance status and low tumor burden (minimal bulky disease in the brain or subarachnoid space). Although there are reports of sustained tumor clearance from the CNS in patients with meningeal involvement from leukemia and lymphoma, overall prognosis is worse than that of patients without leptomeningeal involvement.

**References**


Chamberlain and Chamberlain

Leptomeningeal Metastases


