

Carcinomatous meningitis: Leptomeningeal metastases in solid tumors

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Abstract

Leptomeningeal metastasis (LM) results from metastatic spread of cancer to the leptomeninges, giving rise to central nervous system dysfunction. Breast cancer, lung cancer, and melanoma are the most frequent causes of LM among solid tumors in adults. An early diagnosis of LM, before fixed neurologic deficits are manifest, permits earlier and potentially more effective treatment, thus leading to a better quality of life in patients so affected. Apart from a clinical suspicion of LM, diagnosis is dependent upon demonstration of cancer in cerebrospinal fluid (CSF) or radiographic manifestations as revealed by neuraxis imaging. Potentially of use, though not commonly employed, today are use of biomarkers and protein profiling in the CSF. Symptomatic treatment is directed at pain including headache, nausea, and vomiting, whereas more specific LM-directed therapies include intra-CSF chemotherapy, systemic chemotherapy, and site-specific radiotherapy. A special emphasis in the review discusses novel agents including targeted therapies, that may be promising in the future management of LM. These new therapies include anti-epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors erlotinib and gefitinib in nonsmall cell lung cancer, anti-HER2 monoclonal antibody trastuzumab in breast cancer, anti-CTLA4 ipilimumab and anti-BRAF tyrosine kinase inhibitors such as vemurafenib in melanoma, and the antivascular endothelial growth factor monoclonal antibody bevacizumab are currently under investigation in patients with LM. Challenges of managing patients with LM are manifold and include determining the appropriate patients for treatment as well as the optimal route of administration of intra-CSF drug therapy.

Key Words: Diagnostic tools, leptomeningeal metastases, monoclonal antibody, neoplastic meningitis, solid tumors, tyrosine kinase inhibitors, targeted therapy

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INTRODUCTION

Leptomeningeal metastases (LM) result from metastatic infiltration of the leptomeninges by malignant cells originating from an extrameningeal primary tumor site that

may be extraneural (most common) or intraneural (less common). Cerebrospinal fluid (CSF) dissemination of cancer is an important issue in neuro-oncology because its incidence is increasing and the clinical consequences are profound. Over the past decades, important advances

have been made in earlier diagnosis of the disease but these advances have not been accompanied by substantial therapeutic progress. Patients usually present with pleomorphic and subtle neurological signs affecting the central nervous system (CNS), sometimes difficult to differentiate from those due to brain metastases or adverse effects of cancer treatment. Entire neuraxis magnetic resonance imaging (MRI) is required for diagnosis, but the identification of neoplastic cell by CSF cytological study is the key feature determining LM. The specificity and the sensitivity of MRI and CSF analyses remain poor. Diagnosis notwithstanding the availability of CNS imaging and CSF cytology remains a challenge. New methods for corroborating a diagnosis of LM are under development. Additionally, several prognostic factors have been identified to assist in determining whom to treat with LM-directed therapy. Early detection of LM, before the installation of fixed deficits, is needed to improve the prognosis. Without specific LM-treatment, median survival is limited to several weeks. With combined treatments, the median survival of patients with LM averages several months. Specific treatment of LM typically combines systemic and intrathecal (IT) chemotherapy and site-specific radiotherapy. Choice of intra-CSF chemotherapy may vary according to the site of origination of the primary tumor. New agents are now under evaluation. This review focuses on LM originating from solid tumors excluding leptomeningeal dissemination of hematological malignancies (e.g., leukemia and lymphoma) or primary brain tumors.

EPIDEMIOLOGY

The incidence of clinically diagnosed LM in patients with solid tumors is approximately 5% but the incidence of undiagnosed or asymptomatic LM may be 20% or more with many solid tumors as illustrated in autopsy series.^[73,157,160,185,211,226,227,248,279,289] Although any cancer can metastasize to the leptomeninges, breast cancer (12-35%), lung cancer (10-26%), melanoma (5-25%), gastrointestinal cancer (4-14%), and cancers of unknown primary (1-7%) are the most common causes of solid-tumor-related LM [Tables 1 and 2].^[37,73,157,160,227] In breast cancer, the most common solid tumor to cause LM, risk factors of LM include an infiltrating lobular carcinoma and cancers

negative for estrogen receptor (ER) and progesterone receptor (PR).^[4,169-171,177,108,181] Triple negative status of breast cancer (HER2/neu negative; ER negative; PR negative) has been reported to be a risk factor of LM.^[230] LM involvement is remains a relatively rare manifestation of HER2/neu positive tumors (3-5%) notwithstanding the observed increased incidence of parenchymal brain metastasis.^[181,182]

Treatment of systemic cancer metastatic to the CNS appears to influence the incidence of LM accounting in part for the apparent increase incidence of LM. Among these factors, surgical resection of parenchymal cerebellar metastases has purportedly resulted in subsequent development of LM.^[82,205,245] Resection of a supratentorial brain metastasis that violates the ventricular system also appears to increase the risks of developing LM.^[3,82,96,285] The presumed mechanism in both instances likely is spillage of cancer cells directly into CSF and subsequent dissemination.

Another important factor contributing to an increased incidence of LM is more effective systemic therapy, both adjuvant and salvage, leading to a prolongation of survival and late metastatic spread to the CNS. The use of newer targeted therapies with poor CNS penetration such as trastuzumab (Herceptin used for her2/neu positive cancers) and rituximab (Rituxan used for B-cell malignancies) is another factor that contributes to an increased incidence of LM.^[9,131,168,212]

The meninges and CSF compartment are indeed a pharmacological sanctuary for many cytotoxic agents that poorly cross an intact blood-CSF barrier. In this situation, tumor cells in the subarachnoid space are not adequately treated by systemic cytotoxic therapy and may consequently escape cytotoxic effects of systemic therapy and proliferate as previously observed in acute leukemia prior to the introduction of CNS-directed therapy.

A combination of these factors probably explains the considerable increase in the actuarial incidence of LM in small cell lung cancer (SCLC) over time, from 0.5% at diagnosis to 25% after 3 years of survival and the observation that isolated meningeal involvement is no longer an exceptional site of relapse after chemotherapy for breast cancer, particularly when taxanes or trastuzumab are used, both of which penetrate poorly

Table 1: Distribution of leptomeningeal metastases by type of cancer

Type of cancer	%
Breast carcinoma	12-34
Lung carcinoma	10-26
Melanoma	17-25
Gastrointestinal tract cancer	4-14
Adenocarcinoma of unknown primary	1-7

Table 2: Frequency of leptomeningeal metastatic involvement by type of cancer

Type of cancer	Frequency of LM (%)
Melanoma	22-46
Small-cell lung cancer	10-25
Breast carcinoma	5
Nonsmall-cell lung cancer	1
Head and neck cancer	1

into the CSF.^[9,80,227,240] The increased rate of premortem diagnosis of LM, relying on a higher clinical appreciation of the disease combined with increasing utilization of neuroimaging studies, especially gadolinium-enhanced MRI of the entire neuraxis, also improves identification of this disease.^[240] Occasionally, LM may be detected by MRI when the patient is asymptomatic and the CSF analysis is not contributory. Regardless, the incidence of LM remains higher in most postmortem series compared with clinical studies (e.g., 25% vs. 11% in the National Cancer Institute study of small-cell lung cancer), in part because LM generally occurs late in the course of systemic cancer when nonspecific neurological symptoms such as confusion do not necessarily lead to investigation of the CNS as a potential site of metastatic disease.^[240] As well, LM is often associated with other CNS metastases, particularly in the brain parenchyma (33-75%) or dura (16-37%), which may dominate the clinical picture.^[117,211,227,290] In approximately 20% of all cases of LM, meningeal involvement is the first metastatic site.^[211]

PATHOPHYSIOLOGY AND PATHOLOGY

Cancer cells may invade the meninges through different pathways, depending on histology of the primary tumor.^[119,168,227]

Hematogenous spread

Hematogenous spread to the arachnoid via the arterial circulation, is probably the most common route of metastasis resulting in LM, but appears less common in solid tumors compared with hematological malignancies.^[119,166] Additionally, seeding of the leptomeninges via retrograde venous pathways along the valveless Batson's venous plexus has been incriminated in pelvic cancers but this hypothesis remains speculative.^[35,109]

Endoneural/perineural and perivascular lymphatic spread

Vertebral and paravertebral metastases (particularly from breast and lung cancers) as well as head and neck cancers may spread centripetally along peripheral or cranial nerves^[166] via the endoneural/perineural route or along coassociated lymphatics or veins^[119] gaining access through the dural and arachnoidal sleeves of nerve roots (spinal roots, cranial nerves) and subsequently into the subarachnoid space.

Direct spread from the brain parenchyma

Direct spread from metastases located in the brain parenchyma that is in close opposition to the CSF space has been described. These tumors appear to breach the subarachnoid or ventricular spaces and diffuse widely in the CSF, although a peritumoral fibrotic reaction at the site of invasion often circumscribes this type of metastasis. This manner of spread is particularly relevant with respect to primary brain tumors.^[27]

Choroid plexus

Metastases to the choroid plexus and subependyma has been described with subsequent CSF dissemination though is considered an uncommon mechanism of cancer spread.^[211]

De novo tumors

Primary tumors arising in the meninges such as melanoma and some soft tissue sarcomas (e.g., malignant peripheral nerve sheath tumors) may secondarily spread to the CSF and disseminate.

Iatrogenic spread

During invasive procedures or neurosurgery as mentioned earlier, CSF tumor spread may result through an ependymal or pial breach.^[165,205,285]

Once malignant cells enter the CSF, cancer cells disseminate by extension along the meningeal surface and by convective CSF flow to distant parts of the CNS where random implantation and growth occurs forming secondary leptomeningeal metastatic deposits. While a diffuse covering of the leptomeninges is particularly frequent in hematological malignancies, plaque-like deposits with invasion of the Virchow–Robin spaces and nodular formations are more characteristics of solid tumors. The areas of predilection for circulating cancer cell settlement are characterized by slow CSF flow and gravity-dependent effects (basilar cisterns, posterior fossa, and lumbar cistern).^[27] Malignant cells frequently accumulate sufficiently in the subarachnoid or ventricular compartment and obstruct CSF flow by tumor adhesions at any point along the CSF pathway.^[100]

PATHOLOGY

Gross

Gross inspection of brain, spinal cord, and spinal roots may be normal. More often, however, the leptomeninges are abnormal manifesting thickening and fibrosis that may be diffuse or localized in one or several distinct area(s) of the CNS, particularly in regions with relative CSF flow stasis, as stated earlier.^[146,290]

Microscopic

Characteristically there is diffuse or multifocal infiltration of arachnoid membranes by cancer cells, often filling the subarachnoid and Virchow–Robin spaces, and sometimes invading the underlying neuraxis, vessels, and nerve surfaces. Cranial and spinal nerve demyelination and axonal degeneration are occasionally observed without any tumor infiltration. Microscopic examination may also reveal infarction of infiltrated areas.^[164,289] A pure encephalitic variant is characterized by massive invasion of the Virchow–Robin spaces, without infiltration of the sub-arachnoid spaces of the brain surface.^[188]

The physical–chemical characteristics of the blood–CSF-barrier comprised of ependymal and leptomeningeal (brain/spine) parts, differs from those of the blood–brain barrier (between blood and brain parenchyma).^[68,270,299] Functioning of the blood–CSF-barrier is poorly understood and may differ from that of the blood–brain barrier.

PATHOPHYSIOLOGY OF SIGNS AND SYMPTOMS

Several mechanisms, often combined, are incriminated, which result in the symptom complex characteristic of LM.

Hydrocephalus and increased intracranial pressure

Tumor infiltration of the base of the brain, Sylvian fissures, and arachnoid villi as well as reactive fibrosis and inflammation may impair or block CSF outflow and lead to hydrocephalus and increased intracranial pressure. However, when the site of obstruction is located near the sagittal sinus or basilar cisterns, intracranial pressure may be elevated in the absence of obvious hydrocephalus.^[136]

Compression and invasion

Focal neurological symptoms and signs, and increased intracranial pressure may result from compression or invasion of the brain and spinal cord, as well as cranial and peripheral nerve roots.^[227]

Ischemia

Invasion, compression, or spasm of blood vessels located on the brain convexity or in the Virchow–Robin spaces may interfere with the blood supply and oxygenation of neurons and may produce transient attacks, strokes, and perhaps encephalopathy secondary to a global decrease in cerebral blood flow.^[255]

Metabolic competition

Some patients develop a diffuse encephalopathy of unknown origin and it has been suggested that tumor cells and neurons may be in competition for metabolites such as glucose leading to relative metabolite deprivation of the underlying neurons.^[142]

Blood–CSF barrier disruption

A disruption of the blood–CSF barrier is rarely a consequence of direct invasion by LM but more commonly due to the development of tumoral angiogenesis with associated leaky fenestrated LM-related neovasculature that develops when LM-related tumors reach a threshold diameter (nodules) or thickness (layers).^[290] This process of tumor angiogenesis results in an abnormal blood–CSF barrier as illustrated by contrast enhancement of the involved meninges on MRI. Nevertheless, breakdown of the blood–CSF barrier in LM is incomplete and partial as manifested by the observation that only a minority of patients respond to systemic water-soluble chemotherapy,

even in the instance when other extrameningeal systemic metastases demonstrate response.

DIAGNOSIS OF LM

The diagnosis of LM may be ascertained according to the National Comprehensive Cancer Network (NCCN) guidelines.^[33] The guidelines suggest any one of the following diagnostic criteria are sufficient to diagnose LM; CSF positive for tumor cells (positive CSF cytology); radiologic findings in the CNS consistent with LM irrespective of supportive clinical findings or alternatively and more controversial, clinical signs and symptoms consistent with LM and a nonspecific but abnormal CSF analysis (high white blood cell count, low glucose, and elevated protein) in a patient known to have a cancer. In the majority of studies of patients with LM, LM has been defined by either malignant cells in the CSF or positive neuroradiologic findings consistent with LM and supportive clinical findings. Nonetheless, underdiagnosis remains a major problem in establishing a diagnosis of LM as specific assessments are required (CSF analysis and CNS imaging) and because CSF cytology and neuraxis imaging are often normal.

Clinical features

Patients most often present with pleomorphic and multifocal neurological symptoms and signs related to the specific region of the CNS involved by malignant cells. Symptoms and signs are classically divided into three domains of neurological function: Cerebral hemisphere, cranial nerve and spinal cord, and exiting nerve roots.^[60,127] The neurologic domain-specific incidence at the time of LM diagnosis is illustrated in Table 3. Headache, changes in mental status, difficulty in walking, nausea, and vomiting are the most frequent manifestations of cerebral dysfunction. Diplopia (mostly cranial nerve VI impairment) and facial paresis are the leading and most common symptoms of cranial nerve involvement due to LM. The most frequent spinal manifestations are lower motor weakness, limb paresthesia, back or neck pain, and radiculopathy. Neck stiffness, that is, meningismus is present in less than 15% of all cases of LM.^[8,60,127,151,185,289] The presentation of LM differs from that of bacterial or hemorrhagic meningitis, as fever, photophobia and meningismus are extremely uncommon. Syncope, headache, nausea, and vomiting resulting from impaired CSF resorption and raised intracranial pressure is frequent in LM and may manifest at any time during the course of the disease. Seizures in general are comparatively rare in LM (<10% incidence).

Pleomorphic and multifocal neurological symptoms and signs are strongly suggestive of the diagnosis of LM in patients with known cancer, but patients may also present with isolated and subtle neurologic symptoms. Neurologic dysfunction due to LM should

Table 3: Symptoms and signs at LM diagnosis (adapted from Chamberlain 2009 and Groves 2008)

	Symptoms	%	Signs	%
Cerebral	Headache	51-75	Mental status change	27-65
	Mental change	26-33	Seizure	11-18
	Gait difficulty	27	(Focal/generalized)	(11/6)
	Nausea and vomiting	22-34	Papilloedema	11
	Unconsciousness	4	Sensory disturbance	11
	Dysphagia	4	Insipid diabetes	4
	Coordination disorders	20-34	Hemiparesis	2
	Loss of consciousness	4	Cerebellar disorder	15
	Dizziness	4		
	Cranial nerve	Diplopia	20-36	Ocular motor paresis III, IV, VI
Visual loss		9-10	Facial paresis VII	10-27
Hearing loss		5-14	Visual loss II	5-19
Decreased hearing		5	Optic neuropathy	8
Tinnitus		3	Diminished hearing VIII	7-18
Facial numbness		8-10	Trigeminal neuropathy V	6-10
Hypoguesia		4	Diminished gag reflex IX, X	2-6
Dysphonia/dysphagia		2-7	Hypoglossal neuropathy XII	5-10
Hoarseness		3		
Vertigo		2		
Spinal	Lower motor neuron weakness	34-46	Reflex asymmetry	86
	Paresthesias	33-42	Nuchal rigidity	9-13
	Back/neck pain	31-37	Weakness	73
	Radicular pain	26-37	Sensory loss	32
	Bladder and bowel dysfunction	16-18	Straight leg raising	15
	Upper motor neuron weakness	14	Decreased rectal tonus	5-14

LM: Leptomeningeal metastasis

be distinguished from those due to parenchymal brain metastases, complications of antineoplastic treatments, other causes of chronic meningitis (tuberculosis, fungal infections, sarcoidosis) as well as metabolic and toxic encephalopathies or concurrent diseases.^[58,118,276,289]

Imaging diagnosis

Because LM involves the entire neuraxis, imaging of the entire CNS is required. MRI with gadolinium enhancement is the radiologic technique of choice.^[38,58,246,274]

The standard examination should include at the cerebral level, axial T1-weighted images without contrast, fluid attenuation inversion recovery (FLAIR) sequences and 3D axial T1-weighted sequences with contrast. The spine is best evaluated with sagittal T1-weighted sequences with and without contrast and sagittal fat suppression T2-weighted sequences,

combined with axial T1-weighted images with contrast of regions of interest. Contrast enhanced T1-weighted and FLAIR sequences are the most sensitive to detect LM.^[89,261]

Any irritation of the leptomeninges, such as subarachnoid blood, infection, inflammation can result in enhancement on MRI. Lumbar puncture itself can cause a meningeal reaction, leading to leptomeningeal enhancement. MRI should be obtained preferably prior the lumbar puncture.^[197] At LM diagnosis, brain involvement may be present in 40-75%. MRI in LM may demonstrate subarachnoid, ventricular or parenchymal enhancing nodules, focal or diffuse pial enhancement, ependymal, sulcal, folia, or cranial nerve enhancement. Hydrocephalus, an indirect imaging sign of LM, may also be observed. The most frequent brain MRI findings are subarachnoid nodules (35-50%) and pial enhancement (15-50%). Spine involvement is present in 15-25% of the patients. The most frequent MRI findings are subarachnoid and parenchymal enhancing nodules (10-35%), diffuse or focal pial enhancement (10-20%). Nerve root enhancement can also be observed.^[64] Brain parenchymal metastases may be associated with LM in 21-82%.^[74,199,218,241]

The sensitivity of MRI varied from 20% to 91%.^[64,73,84,108,199,218,241,298] A normal MRI does not exclude the diagnosis of LM. Nonetheless in cases with a typical clinical presentation, abnormal MRI alone is adequate to establish the diagnosis of LM as stated earlier.^[60,62,64]

CT is of limited value in the diagnosis of LM.^[89] The sensitivity of computed tomography (CT) scan is estimated at 23-38%, and CT scan should be reserved only for patients unable to undergo MRI.^[108,274]

Radionuclide studies using ¹¹¹Indium-diethylene-triamine pentaacetic or ⁹⁹Tc macro-aggregated albumin represent the techniques of choice for the evaluation of CSF flow interruption. In patients with LM, CSF flow blocks may be present in 30-70% of patients, mostly occurring at the skull base, within the spine and over the cerebral convexities.^[39,42,46,47,50,111,123,190] CSF flow blocks are a consequence of tumor adhesions in the subarachnoid space. Patients with CSF flow interruptions have been shown to have a decreased survival compared with those with normal CSF flow.^[42,46,111,123] In the presence of CSF flow blocks, intra-CSF treatment has reduced efficacy and increased toxicity due to impaired intra-CSF drug distribution.^[190] Administration of involved-field radiotherapy to the site of CSF flow obstruction restores flow in 30% of patients with spinal involvement and in 50% of patients with intracranial involvement.^[50] After reestablishment of CSF flow, the survival of patients with pretreatment CSF flow interruption is similar to patients without flow abnormalities.^[39,42,50,111,122,190]

CSF examination

Abnormalities of the standard CSF analysis are observed in more than 90% of the cases of LM.^[62] These abnormalities include increased opening pressure (>200 mm of H₂O) in 46%, increased leukocytes (>4/mm³) in 57%, elevated protein (>50 mg/dl) in 76%, and decreased glucose (<60 mg/dl) in 54%. Although indicative of LM, these CSF abnormalities are nonspecific. Identification of cancer cells in the CSF by cytological analysis is the key diagnostic feature of LM.^[60,62] The sensitivity of a first lumbar puncture is estimated at 45-55%, but can be increased to 80% with a second CSF examination.^[60,62] Little benefit is obtained from a third CSF examination.^[117,157,289]

Several simple procedures can improve the sensitivity of the CSF cytological analysis including submission of a nonhemorrhagic CSF specimen. In a series of patients with LM demonstrated by positive lumbar CSF cytology and without any evidence of CSF flow obstruction, ventricular and lumbar cytology obtained simultaneously were discordant in 30% of cases.^[51] Not obtaining CSF samples from a site that is symptomatic clinically or radiologically may result in false-negative CSF cytology, according to a prospective study.^[112] Obtaining large CSF sampling volumes (>10.5 ml) improves the yield of CSF sensitivity. The sensitivity of CSF cytology increased from 68% to 97% for 3.5 and 10.5 ml samples, respectively.^[112] Processing of CSF specimens in a timely manner is also critical to improve the sensitivity of CSF cytology. The viability of cells depends on time between sampling and laboratory examination: After 30 minutes, 50% of the cells remain viable, and only 10% of cells remain viable after 90 minutes.^[94] The role of CSF fixation in dedicated tubes should be validated. Nonetheless, there remains a group of patients (approximately 25-30%) with LM defined by a clinical syndrome, normal neuraxis imaging, and persistently negative CSF cytology.^[62,84,108,176,241]

A variety of biomarkers of LM have been suggested to assist in achieving an earlier diagnosis of LM and to evaluate effectiveness of treatment. These biomarkers may be nonspecific, such as β -glucuronidase, lactate dehydrogenase, beta2-microglobulin, carcinoembryonic antigen or alternatively organ specific such as CA 15-3, CA 125, CA 19-9, CA724, AFP, NSE, Cyfra 21-1, and EGFR. CSF release of tumor biomarkers markers has been demonstrated in many patients with LM, however, there was no clear correlation with the type of carcinoma or response to treatment observed.^[48,79,107,108,121,156,251,253,286] Emerging biomarkers for LM such as proangiogenic molecules (vascular endothelial growth factor [VEGF], urokinase plasminogen activator (uPA), and tissue plasminogen activator (tPA)) have also been evaluated. In the majority of studies, VEGF levels were increased in patients with LM, but sensitivities (51.4-100%) and specificities (71-100%) have varied widely.^[28,79,121,128,141,269,284]

Combinations of different markers have been suggested to increase the sensitivity of CSF biomarkers in LM.^[128] Profiling CSF proteins and in particular those involved in the metastatic process, may have potential diagnostic and prognostic value. Protein assays have used mass spectrometry and multiplex immunoassay.^[29,86,121,239] Another new promising method using the Cellsearch technology (identification of cell surface tumor associated proteins) may allow the identification and the quantification of malignant cells in the CSF in LM.^[219] Further evaluations of this technology with a simplified method are now ongoing.

At present there is neither agreement regarding CSF biomarker cutoff levels nor has there been standardization of CSF sampling and processing. Due to inconsistencies in laboratory methodology, there is considerable variations in sensitivity and specificity of these assays that represent serious challenges for utilizing biomarkers in the management of LM.^[60,129,294] At present, the gold standard in diagnosing LM remains the detection of tumor cells in the CSF by CSF cytology.

EVALUATION AND RESPONSE TO TREATMENT

No standardized criteria to evaluate the response to treatment of LM have been defined or universally agreed upon. New clinical signs and symptoms must be distinguished from manifestations of parenchymal disease, from side-effects of intra-CSF treatment, systemic treatment or radiation, from co-medications, from neurological or extraneurological concurrent disease, and more rarely from paraneoplastic syndromes.^[58] Transient neurological deficits or symptoms should not be misconstrued as LM-related neurological progression. The one-dimensional response evaluation criteria in solid tumors (RECIST) criteria are not appropriate for the evaluation of LM as the imaging features of LM (subarachnoid, ventricular or parenchymal enhancing nodules, focal or diffuse pial enhancement, ependymal, sulcal, folia or cranial nerve enhancements) in general are not measurable at least as defined by current brain tumor response criteria.^[186,293]

As mentioned earlier, CSF cytological analysis remains the gold standard for the identification of malignant cells in the CSF. The sensitivity of a first CSF examination varied from 45% to 55%, and usually, two successive CSF samples are required to adequately assess cytology. The majority of clinical trials in LM have utilized a combination of CSF cytology (conversion from positive to negative) and clinical response (improved or stable) to determine success of LM-directed treatment. At present there are no agreed upon radiographic criteria to determine response to treatment in LM. Consequently, new consensual response criteria are needed in LM so

as to better adjudicate outcome and to permit more uniform conduct of clinical trials with novel agents.

SURVIVAL AND PROGNOSTIC FACTORS

The median overall survival (OS) of untreated patients with LM is 4-6 weeks.^[32,42,44,45,55,56,58,59,61,62,74,129,137,151,180,213,216,229,250,254,265,288,298] Despite aggressive treatment, LM has a poor prognosis. The survival of patients with combined treatment is usually less than 8 months with a median OS of 2-3 months.^[45,73,74,84,108,137,199,218,241,298] Table 4 illustrates reported survival in patients with LM from the recent literature.

The aim of LM-directed treatment is to improve or stabilize the neurological status, maintain neurological quality of life, and prolong survival. Nonetheless, deciding

which patients to treat with LM remains challenging. The NCCN CNS guidelines (version 1.2012) have attempted to distinguish between patients reasonably considered for treatment vs. those patients in whom supportive care is most appropriate [Table 5].^[32,42,44,47,55,56,60,62]

Based on the literature, the type of primary cancer is known to be the major prognostic factor with regard to OS in LM.^[60,276] Multivariate analysis has confirmed the association between OS and primary tumor type and the better prognosis of breast cancer compared with lung cancer or melanoma-related LM.^[73,141,208] Breast cancer LM has a relatively good prognosis among all solid tumor-related LM, with a median OS of 3.3-5 months.^[74,84,108,176,241] Modest improvement in lung cancer-related LM may in part reflect increasing use of targeted agents such as tyrosine kinase inhibitors (TKI)

Table 4: Median OS in the main cohorts of LM according to the primary type of tumor

Type of the primitive tumor	References	Recruitment of the patients	Median overall survival (Min-Max)
All types	Wasserstrom <i>et al.</i> , 1982	90 patients from 1975 to 1980	5.8 months (1-29)
	Hitchins <i>et al.</i> , 1987	44 patients	8 weeks
	Liaw <i>et al.</i> , ^[179] 1992	41 patients from 1984 to 1990	4 weeks
	Grossman <i>et al.</i> , 1993	52 patients	14.1-15.9 weeks
	Chamberlain 2002	22 patients from 1995-2001	16 weeks
	Glantz <i>et al.</i> , 1999	61 patients from 1994 to 1996	78-105 days
	Kim <i>et al.</i> , 2003	55 patients from 1995 to 2002	11.9 weeks (2.7-28.7)
	Herrlinger <i>et al.</i> , 2004	155 patients from 1980 to 2002	4.8 months
	Lassman <i>et al.</i> , ^[174] 2006	32 patients from 1999 to 2003	19.9 weeks (2.9-135.4)
	Groves <i>et al.</i> , 2008	62 patients from 2001 to 2006	15 weeks (95% CI, 13-24w)
	Waki <i>et al.</i> , 2009	85 patients from 1995 to 2005	51 days (3-759 days)
	Clarke <i>et al.</i> , 2010	187 patients from 2002 to 2004	2.4 months (95% IC 1.9-3.1)
	Oeschle <i>et al.</i> , 2010	135 patients from 1989 to 2005	2.5 months
	Jimenez Mateos <i>et al.</i> , ^[153] 2011	37 patients from 1990 to 2008	12.6 weeks
	Gani <i>et al.</i> , ^[106] 2012	27 patients	8.1 weeks
Segura <i>et al.</i> , 2012	19 patients	43 days (95% IC 28-57.3)	
Breast cancer	Boogerd <i>et al.</i> , 2004	35 patients from 1991 to 1998	18.3-30.3 weeks
	Grossman 1982	52 patients	14.1-15.9 weeks
	Clamon <i>et al.</i> , ^[71] 1987	22 patients	21-150 days
	Boogerd 1991	58 patients	12 weeks
	Jayson ^[152] 1994	35 patients	77 days
	Chamberlain 1997	32 patients	7.5 months (1.5-16)
	Jaeckle 2001	43 patients from 1994 to 1999	7 weeks
	Regierer ^[231] 2008	27 patients from 1998 to 2005	9 weeks
	Rudnicka <i>et al.</i> , 2007	67 patients from 2000 to 2005	16 weeks (1-402)
	De Azevedo <i>et al.</i> , 2011	60 patients from 2003 to 2009	3.3 months (0.03-90.4)
	Clatot <i>et al.</i> , 2009	24 patients from 1999 to 2008	150 days (9-561)
	Gauthier <i>et al.</i> , 2010	91 patients from 2000 to 2007	4.5 months (0-53)
	Lee <i>et al.</i> , 2011	68 patients from 1995 to 2008	4.1 months (2.2-5.8 months)
Kim <i>et al.</i> , ^[163] 2012	30 patients from 1981 to 2009	8 months	
Melanoma	Chamberlain <i>et al.</i> , 1996	16 patients from 1986-1995	4 months
	Harstad 2008	110 patients from 1944 to 2002	10 weeks (95% IC, 8-14)
Lung cancer	Rosen <i>et al.</i> , 1982	60 patients from 1969 to 1980	7 weeks
	Chamberlain <i>et al.</i> , 1998	32 patients	5 months (1-12)
	Hammerer ^[135] 2005	26 patients	57 weeks (NA)
	Sudo <i>et al.</i> , ^[272] 2006	37 patients from 2001 to 2005	106 days (10-392)
	Chuang <i>et al.</i> , ^[70] 2008	34 patients from 1992 to 2002	5.1 weeks (1 day-82 weeks)
	Morris 2012	50 patients from 2003 to 2009	3 months (95% IC, 2.0-4.0)
	Park 2012	125 patients from 2002 to 2009	4.3 months (1.5-6.7)

Table 5: Risk categories in patients with in leptomeningeal metastases (adapted from CNS national comprehensive cancer network guidelines)

Poor risk group	Good risk group
Low KPS (<60%)	High KPS (≥60%)
Multiple, serious, or major neurological deficits	No major neurological deficits
Extensive systemic disease with few treatment options	Minimal systemic disease
Bulky CNS disease	Reasonable systemic treatment options
LM-related encephalopathy	No CSF block

KPS: Karnofsky performance status, CNS: Central nervous system

based on recent reports of patients with lung cancer and LM with reported median survival of 3-4.3 months.^[199,218] Melanoma complicated by LM continues to demonstrate the worst prognosis of all solid tumor-related LM with a median OS estimated at 10 weeks before the era of the immunotherapy.^[137]

In addition to tumor histology, multivariate analysis confirms the association between OS and the performance status (PS), the age at LM diagnosis and the treatment modality (administration of systemic therapy).^[59,73,141,208] In one report, gender was significant in multivariate analysis likely due to an interaction between gender and tumor type.^[73] In patients with breast cancer and LM, multivariate analysis demonstrates an association between OS and PS as well as PS and treatment modalities (number of prior chemotherapy regimens, receipt of combined treatment modality, coadministration of systemic chemotherapy, and intra-CSF chemotherapy). Histological characteristics (histological grade and hormone receptor status), the number of prior chemotherapy regimens, status of systemic disease (i.e., isolated CNS metastases), the initial response to treatment, cytologic response to treatment and in one study, the CSF cyfra 21-1^[108] level were also identified as significantly associated with prognosis in breast cancer-related LM.^[74,84,108,176,241]

In a recent study of patients with lung cancer and LM, multivariate analysis confirmed that PS, the treatment modality (especially systemic therapy), clinical improvement after intra-CSF chemotherapy were all significantly associated with a better OS.^[218] Intra-CSF chemotherapy appeared to improve OS in a recent case series of patients with lung cancer and LM.^[199] The impact of whole brain radiotherapy is unclear though a recent study suggests that when administered as a single modality of treatment for patients with lung cancer and LM, OS was not improved. In a small group of patients with EGFR mutations, LM, and lung cancer, EGFR inhibitors had an apparent durable benefit for patients with LM and sensitive EGFR mutations.^[72,158,191,199,218,287,296] In patients with melanoma, multivariate analysis suggests that a history of a primary melanoma lesion originating

on the trunk predicted shorter OS, and that intra-CSF chemotherapy predicted longer OS.^[137]

TREATMENT

The goals of treatment include palliating neurologic symptoms and whenever possible stabilizing or improving patient neurologic function as well as prolonging survival. Since the prognosis of LM varies noticeably depending upon the primary tumor type and extent of both neurologic and systemic disease, parameters separating poor-risk from good-risk patients are helpful to determine the appropriate therapeutic approach for an individual patient. The poor-risk and good-risk patients categories are illustrated in Table 4. LM ideally should be diagnosed early in the disease course before the appearance of fixed and disabling neurological deficits. Early LM-directed treatment may allow maintenance of quality of life and potentially improve survival. A combined treatment approach (i.e., systemic and intra-CSF chemotherapy and site specific radiotherapy) may provide better palliation in patients with LM.

Symptomatic

Patients with low PS, quality of life interfering fixed neurologic deficits or encephalopathy due to extensive LM-brain infiltration, and uncontrolled systemic disease with limited therapeutic options have a poor prognosis even with active LM-directed treatment. A palliative approach should be considered in such poor prognosis patients.^[54,56] Regardless, however, supportive care is needed in every patient with LM independent of treatment in order to palliate and when possible treat neurological symptoms and signs associated with LM.

Treatment of LM-related pain that may include headache, back, or radicular pain, frequently necessitates using opioid analgesics. In addition, neuropathic pain often requires tricyclic antidepressants (such as amitriptyline or nortriptyline) or antiepileptic drugs (such as gabapentin, pregabalin, carbamazepine, and lamotrigine). Corticosteroids may also improve radicular pain. Focal irradiation of symptomatic sites is often quite efficient in relieving pain. Seizures are managed with anticonvulsant drugs (AEDs) but prophylactic administration of AEDs is not recommended in patients who have never had seizures. Headaches related to edema or increased intracranial pressure can sometimes be managed with steroids, even if the contribution of steroids in the treatment of LM is modest as compared with their efficacy in brain parenchymal metastases. In instances of hydrocephalus secondary to CSF block, a course of steroids during whole brain or skull-base radiotherapy is sometimes useful but CSF shunting is often required in this situation.^[83,111] Repeated lumbar punctures in the absence of threatening associated brain metastases may be an alternative method to

relieve temporarily headache in patients declining CSF diversion. Depression or fatigue may be managed with serotonin reuptake inhibitors or stimulant medication (modafinil, methylphenidate) as clinically appropriate. Last a discussion of end of life before institution of LM-directed therapy is recommended in all patients so as to realistically outline the course of disease and palliative treatment goals.

Surgery

The main surgical intervention in LM is ventriculoperitoneal shunting (VPS) for symptomatic hydrocephalus and placement of a ventricular (rarely lumbar) access device (e.g., an Ommaya or Rickham reservoir) to facilitate administration of intra-CSF chemotherapy. When both a VPS and Ommaya ventricular access device are needed, an on-off valve may be placed but this necessitates that the patient can tolerate having the VPS placed in the off position so as to permit drug installation into the ventricles and time for ventricular transit and distribution into the nonventricular CSF compartments.^[83,183] Complications of VPS include the potential for peritoneal dissemination of the tumor, device failure, and infection.

When a ventricular access device is placed, confirmation postimplantation of correct intraventricular (IVent) placement requires a brain CT or alternatively a radio-isotope CSF flow study before intra-CSF drug administration.^[187,207,273] Hemorrhage at the time of device placement occurs in less than 1% of patients. Device infection is due mainly to *Staphylococcus epidermidis* and complicates about 4-10% of surgical procedures as well as a similar number following surgery that result from contamination at the time of device access.^[207,259,273] In instances where the ventricular device becomes infected, the IVent device may be left *in situ* and treated with both intravenous and IVent antibiotics.^[47,90,256,259] Most often, however, device infections requires removal and if indicated, replacement of the reservoir.^[281] An unusual complication in patients with increased intracranial pressure, is CSF tracking along the catheter, resulting in subgaleal or intraparenchymal collections of CSF, which may become symptomatic and require revision or replacement with a ventriculoperitoneal shunt.^[290]

Radiation therapy

Craniospinal axis irradiation (CSI) is the only method of radiotherapy that treats the entire neuraxis and that may be reasonably considered as a single modality of treatment for LM. However, in the majority of adults CSI is rarely considered as most patients have previously had some region of the neuraxis irradiated and as well have poor bone marrow reserve as a consequence of prior exposure to cytotoxic chemotherapy. Consequently, CSI and treatment-associated toxicities of myelosuppression and enteritis is deemed too toxic for routine use in adults

with solid tumor-related LM. The role of alternative methods of CSI such as tomotherapy and proton radiotherapy, which could permit improved precision in radiation dosing and targeted volumes and consequently less hematological toxicity, has not been formally evaluated and may be an option in the future.

The majority of patients with LM receive involved-field radiotherapy to sites of symptomatic disease, bulky disease observed on MRI and to sites of CSF flow block defined by radioisotope ventriculography. Irradiation permits tumor masses not treated by intra-CSF chemotherapy (due to limited diffusion of intra-CSF chemotherapy) to receive palliative radiotherapy.^[17] Whole brain irradiation (WBRT) is generally administered at a dose of 30 Gy delivered in 10 fractions over 2 weeks. It provides effective relief of pain and stabilizes neurological symptoms but rarely leads to significant neurological recovery (due to demyelination, axonal and neuronal injury, and injury by infiltrating cancer cells), aspects that commend the need for early treatment of LM.^[206] Regardless of findings by MRI (e.g., the absence of visible radiographic disease), lumbosacral irradiation is indicated in instances of symptomatic involvement of the cauda equina (low back pain, legs weakness, bladder or bowel dysfunction). Similarly, skull-base radiation therapy (RT) may be used in patients with cranial neuropathies.^[227] Radiotherapy is also indicated to reestablish normal CSF following documentation of CSF flow blocks to permit improved efficacy and decreased toxicity of intra-CSF chemotherapy.^[42,157,185,211,226,249,279,289] Communicating hydrocephalus is not infrequent in LM and is caused by malignant cells in the subarachnoid space that obstruct normal CSF resorption pathways. In these instances, WBRT or placement of a VPS are often required.^[66] Shunting of CSF should be provided in patients with symptomatic or communicating hydrocephalus that does not rapidly respond to WBRT. Unlike brain metastases, the impact of WBRT on OS is not clearly established in LM, even in radiosensitive cancers such as breast cancer and NSCLC. Contradictory results have been reported that in part reflects the limited survival of patients with LM (<15% survive 1 year).^[199,218]

Major side effects secondary to involved-field RT alone are uncommon aside from radiation-associated fatigue. However, major effects such as myelosuppression, mucositis, esophagitis, and leukoencephalopathy have been reported with more extensive radiation fields. Leukoencephalopathy (asymptomatic more often than symptomatic) may be a delayed consequence in patients treated by concomitant WBRT and methotrexate (MTX) (either systemic or intra-CSF). Ongoing clinical trials evaluating the safety of concomitant WBRT and intra-CSF liposomal cytarabine (ara-C) will define if this is a common problem with chemoradiation or unique to MTX when combined with radiotherapy.

Other types of RT consisting of intra-CSF administration of radioisotopes^[81,91,194] or radiolabeled monoclonal antibodies have been utilized but are considered experimental.^[10,167,200]

Chemotherapy

Chemotherapy is the only modality aside from CSI allowing simultaneous treatment of the entire neuraxis.^[18,19,228] Chemotherapy can be administered intrathecally or systemically.

Intra-CSF chemotherapy

Intra-CSF (intralumbar or IT and IVent) chemotherapy is the mainstay of treatment for LM, although its superiority compared with systemic treatment has not been established in randomized trials and its efficacy consequently is uncertain [Table 6]. Nevertheless, recent retrospective data suggested that intra-CSF chemotherapy may have utility in NSCLC patients, a poor prognosis population that is not often treated with intra-CSF chemotherapy treatment.^[199,218] Park reported 48 patients with NSCLC-related LM who received intra-CSF chemotherapy with a cytological response rate of 52%. The median survival was 5.5 months in cytological responders and 1.4 months in nonresponders ($P = 0.075$).

Morris reported an 18 months median survival (range, 5-33 months) in the seven patients with LM secondary to NSCLC selected to receive intra-CSF chemotherapy.^[199] These results appeared superior to those not selected for this treatment ($P = 0.001$) in a landmark analysis. However, due to the limited number of patients, heterogeneous regimen of intra-CSF treatment and retrospective nature, these data should be interpreted with caution.

The normal blood-brain and blood-CSF barriers limit penetration into the CNS of most systemically administered anticancer agents. Consequently, CSF exposure to most cytotoxic agents is less than 5% of the plasma concentration. The blood-CSF barrier in LM is compromised but the disruption is partial, varies from one region to another such that with few exceptions (e.g., high-dose MTX discussed later for breast cancer-associated LM) is rarely a primary treatment of LM.

The goal of intra-CSF chemotherapy is therefore to bypass the blood-CSF barrier, maximizing drug exposure in the CSF while reducing systemic toxicity. With this approach, a higher drug concentration can be achieved using a smaller dose, because the distribution volume of CSF

Table 6: Randomized studies in leptomeningeal metastases secondary to solid tumors

Study	Design	Response	Toxicity
Boogerd	$N=35$ Breast cancer IT vs. no IT [†]	IT MTX vs. no IT MTX: Improvement or stabilization: 59% vs. 67% TTP: 23 vs. 24 wk Median survival: 18.3 vs. 30.3 wk	IT MTX vs. no IT MTX: Neurological complications: 47% vs. 6%
Glantz	$N=28$ Lymphoma DepoCyt vs. Ara-C	IVent DepoCyt vs. IVent Ara-C: TTP*: 78.5 vs. 42 d OS*: 99.5 vs. 63 d RR: 71% vs. 15%	IVent DepoCyt vs. IVent Ara-C: Headache: 27% vs. 2%; nausea: 9% vs. 2%; fever: 8% vs. 4%; pain: 5% vs. 4%; confusion: 7% vs. 0%; somnolence: 8% vs. 4%
Glantz	$N=61$ Solid tumors DepoCyt vs. MTX	IVent DepoCyt vs. IVent MTX: RR*26% vs. 20% OS*105 vs. 78 d TTP 58 vs. 30 d	DepoCyt vs. MTX: Sensory/motor: 4% vs. 10%; altered mental status: 5% vs. 2%; headache: 4% vs. 2%
Grossman	$N=59$ Solid tumors and lymphoma (in 90%) IT MTX vs. thiotepa	IT MTX vs. IT thiotepa: Neurological improvements: none Median survival: 15.9 vs. 14.1 wk	IT MTX vs. thiotepa: Serious toxicities similar between groups. Mucositis and neurological complications more common in MTX group
Hitchins	$N=44$ Solid tumors and lymphomas IT MTX vs. MTX + Ara-C	IT MTX vs. IT MTX+Ara-C: RR*: 61% vs. 45% Median survival*: 12 vs. 7 wk	IT MTX vs. IT MTX + Ara-C: N/V: 36% vs. 50%; septicemia, neutropenia: 9% vs. 15%; mucositis: 14% vs. 10%; pancytopenia: 9% vs. 10%. AEs related to reservoir: Blocked Ommaya: 17% vs. 0%; intracranial hemorrhage: 11% vs. 0%
Shapiro	Solid tumors ($n=103$) DepoCyt vs. MTX Lymphoma ($n=25$) DepoCyt vs. Ara-C	IVent DepoCyt vs. IVent MTX/Ara-C: PFS*: 35 vs. 43 d DepoCyt vs. MTX: PFS: 35 vs. 37.5 DepoCyt vs. Ara-C: CR*: 33.3% vs. 16.7% PFS: 34 vs. 50 d	IVent DepoCyt vs. IVentMTX/Ara-C: Drug-related AEs: 48% vs. 60% Serious AEs: 86% vs. 77%

*No significant differences between groups, [†]Appropriate systemic chemotherapy and/or radiotherapy given in both arms, AE: Adverse event, Ara-C cytarabine, CR: Complete response, d: day, MTX: Methotrexate, N/V: Nausea/vomiting, OS: Overall survival, PFS: Progression-free survival, RR: Response rate, TTP: Time to progression, wk: Weeks, IVent: Intra-ventricular chemotherapy, IT: Intra-lumbar chemotherapy

is lower than that of the plasma (140 vs. 3500 ml).^[225] Furthermore, the half-life of most cytotoxic agents is longer in the CSF than in plasma, leading to prolonged CSF drug exposure that is particularly useful for cell-cycle specific agents such as MTX and ara-C. The majority of affected regions in LM are only a few cells in thickness and the diffusion capacity of the intra-CSF drug (1-2 mm) is therefore appropriate for treating small volume disease as well as cells suspended in the CSF water column.^[10,36] However, intra-CSF chemotherapy cannot reliably treat bulky leptomeningeal disease because of limited diffusion into tumor lesions 2 mm diameter or more, into the Virchow–Robin spaces and along nerve root sleeves.

Lumbar intrathecal or intraventricular route of administration

IT treatment can be delivered by repeated spinal punctures. Position affects ventricular drug levels after intralumbar administration and patients should remain flat for at least 1-hour following treatment.^[15] On only rare occasion is IT drug administration delivered through a lumbar catheter connected to a subcutaneously implanted reservoir as these devices frequently fail with repeated use.

IVent administration of intra-CSF drug via an Ommaya or Rickham reservoir offers several advantages compared with IT therapy.^[112] The procedure is painless for the patient and more time efficient for the physician. It also provides certainty that the drug has not been administered in the epidural or subdural space (up to 10% of all IT injections), and can be used safely with a platelet count as low as 20,000 cell/mm³, thus avoiding the significant risk of epidural or subdural hematoma after lumbar puncture.^[171] IVent administration also offers several pharmacokinetic advantages over repeated lumbar punctures including better and more uniform drug distribution in the entire subarachnoid ventricular spaces and over the brain convexities.^[41,161,248] IVent CSF drug concentration following IT injection is only 10% of these achieved after an equivalent IVent dose. It also offers the possibility of delivering frequent small doses of drug to reduce high peak drug concentrations and therefore limit total cumulative drug dose that may translate as less neurotoxicity. A survival benefit was suggested for IVent compared with IT chemotherapy in one randomized clinical trial.^[145] IVent and IT administrations were compared in a subset analysis of a randomized trial comparing liposomal ara-C with MTX in 100 patients with LM.^[116] Overall, intra-CSF chemotherapy was given by IVent and IT route in 72% and 28% of cases, respectively. For patients given liposomal ara-C, there was no statistically significant difference in progression-free survival (PFS) according to the route of administration. For those given MTX, the IVent route appeared superior (PFS 19 vs. 43 days, $P = 0.048$) suggesting that the site of administration affects survival outcome and is dependent upon the CSF half-life of the chemotherapy.

Techniques of intra-CSF administration

Even in asymptomatic patients, it is critical to avoid any variation in CSF volume in these fragile patients recognized to be on the edge of their CSF ventricular “pressure-volume” compliance curve. If the total CSF volume is increased, severe intracranial hypertension can occur. Thus equivalent volume of CSF should be removed (so called isovolumetric withdrawal) prior chemotherapy administration. During the withdrawal of a large volume of CSF from the ventricles, a transient retro-orbital or frontal headache may result. The headache is often improved with administration of intra-CSF chemotherapy if given in 5-10 ml volume. No prospective trials in adults with LM have proven any benefit to concomitant use intra-CSF glucocorticoids (hydrocortisone) in combination with intra-CSF chemotherapy.

Drugs available for intra-CSF treatment

Currently, MTX, liposomal ara-C, and less often thiotepa are used in daily practice. Unfortunately, these drugs are not effective against many of the most frequent solid cancers associated with LM, particularly melanoma and lung cancer. New agents including monoclonal antibodies are currently being investigated in clinical trials and are discussed later.

Methotrexate

Therapeutic CSF concentrations, at 1 μM or more during 48-72 h, are obtained with a 12 mg IT dose of MTX in adults and in children aged older than 2 years.^[18,19,167,248,249] Usually, MTX is initially administered on a twice-weekly schedule for 4 weeks, followed by a decrease in frequency over a total treatment time of 3-6 months. The exact duration of treatment has not been established, but some patients may benefit from prolonged treatment. Alternative schedules have been proposed such as the administration of IVent MTX at 2 mg for 5 consecutive days every 2 weeks.^[19,40,202,222] A dose intense regimen of MTX (15 mg/day, 5/7 days, 1 week on 1 week off) has been explored retrospectively in breast cancer patients with a reported median survival of 4.5-5 months.^[74,101,108] Intra-CSF MTX converts tumor positive CSF to negative in 20-61% of patients with LM.^[113,123,257] The clinical efficacy of different schedules of MTX in retrospective breast cancer LM studies is illustrated in Table 7. This table as well reflects coadministered CNS-directed RT given as part of the LM treatment regimen, which makes the interpretation of the impact of one intra-CSF MTX regimen vs. another challenging.^[113,123,223,244,257] Achieving a cytological response within the first month of IT MTX treatment may be predictive of a better median additional survival (6 vs. 2 months).^[244] Regardless, OS is within a similar range irrespective of the intra-CSF MTX schedule as reported in these various series. Considering the short survival of patients with LM and the difficulty differentiating with certainty the respective roles of radiation and intra-CSF chemotherapy, quality of life

Table 7: Intra-CSF chemotherapy regimens in breast cancer

Agent/ reference	Recruitment of the patients	Population characteristics	Associated treatment	Clinical, MRI and cytologic response	Median OS
STD MTX Rudnicka 2007	67 patients from 2000 to 2005	Median age: 49 Median initial IK>60: 41% CLI: 33%-IDC: 34% HR+: 55% HER2+: Not stated Triple negative: Not stated	Systemic CT*: 61% CNS RT: 64%	Clinical response: NS MRI response: NS Cytol. response: NS Overall response: 76%	4 months
STD MTX Rameri 2011	60 patients from 2003 to 2009	Median age: 46 Median initial PS: Not stated IDC: 78,3% ER+: 51,7%-PR+: 43,3% HER2+: 15% Triple negative: Not stated	Systemic CT: 43% CNS RT: 36,7%	Clinical response: NS MRI response: NS Cytol. response: NS	3.3 months
Int MTX Clatot 2009	24 patients from 1999 to 2008	Median age: 49 Median initial PS: 2 (0-2: 71%) CLI: 29%-IDC: 58% HR+: 58% HER2+: 29% Triple negative: Not stated	Systemic CT: 46% CNS RT: 46%	Clinical response: 96% MRI response: NS Cytol. response: 46%	5 months
Int MTX Gauthier 2010	80 patients from 2000 to 2007	Median age: 53 Median initial PS: Not stated CLI: 28%-IDC: 63% ER+: 70%-PR+: 4% HER2+: 10% Triple negative: 21%	Systemic CT: 78% CNS RT: 29%	Clinical response: 73% MRI response: NS Cytol. response: 20%	4.5 months (0-53)
LIP CYT. Zairi 2012	103 patients from 2007 to 2011	Median age: 48 (25-78) Median initial PS: 2 (0-2: 61%) ILC: 28.7%-IDC: 71.3% ER+: 61.1%-PR+: 44.6% HER2+: 12.6% Triple negative: 23.3%	Systemic CT: 58.2% Whole brain RT: 13.5%	Clinical response: 56.8% MRI response: 62.5% Cytol. response: 30.6%	3.9 months (1 day-33.33 months)

ILC: Invasive lobular carcinoma, IDC: Invasive ductal carcinoma, ER: Estrogen receptors, PR: Progesterone receptors, CT: Chemotherapy, RT: Radiotherapy, NS: Not stated

should be the priority when it comes to the treatment of LM [Table 7].

MTX is eliminated from the CSF by CSF/venous resorption and subsequent delivery into the systemic circulation. Consequently factors that interfere with CSF resorption increase intra-CSF MTX-related neurotoxicity. Similarly renal insufficiency resulting in delayed excretion of MTX or the presence of pleural or peritoneal effusions that create a “third space effect” and thereby accumulation of MTX, can increase systemic MTX toxicity resulting in myelosuppression or mucositis. The coadministration of drugs that displace MTX from albumin such as aspirin, phenytoin, sulfonamides, and tetracycline, may also increase MTX toxicity. Neurologic complications of intra-CSF MTX include aseptic meningitis, acute encephalopathy, transverse myelopathy, and delayed leukoencephalopathy.^[22] Folinic acid (leucovorin) has been suggested to mitigate systemic MTX toxicity and is often prescribed and given orally 10 mg every 6 hours for 1-2 days after each intra-CSF MTX administration. Leucovorin does not cross the blood–brain barrier in sufficient amounts to interfere with the efficacy of intra-CSF MTX.

An accidental overdose of intra-CSF MTX may result in significant morbidity or death. Standard recommendations in such clinical situations include immediate drainage of CSF via lumbar puncture, ventriculostomy with ventriculo-lumbar perfusion, systemic steroids, and systemic leucovorin administration. A potentially useful antidote, the carboxypeptidase-G2 (CPDG2) has been reported. Pharmacokinetic studies showed a 400-fold decrease in CSF MTX concentrations within 5 minutes of CPDG2 administration.^[1]

Cytosine arabinoside (Cytarabine)

ara-C is initially administered at a dosage of 25-100 mg twice weekly and used in a similar manner to that of MTX with a 4-week induction, followed by 4 weeks of consolidation and subsequent maintenance. The half-life of ara-C is much longer in the CSF than in serum because of the low levels of CSF cytidine deaminase, the main catabolic enzyme of ara-C. The rapid deamination observed in the systemic circulation causes minimal systemic toxicities. A concentration times time regimen of intra-CSF ara-C has also been reported.^[300] Liposomal ara-C, a depot encapsulated formulation (DepoCyt)

is the preferred intra-CSF agent in patients with LM secondary to solid tumors as conventional ara-C is relatively ineffective due primarily to the short half-life of ara-C (approximately 3.4 hours). Intra-CSF administration of the conventional formulation of ara-C results in complete clearance of the drug from the CSF within 1 or 2 days.^[97,104] In contrast, liposomal ara-C (Depocyt) with a half-life of 140 hours provides a therapeutic ara-C concentration in the CSF for up to 10-12 days. Due to the long half-life of liposomal ara-C, intra-CSF drug administration may be once every 2 weeks. At present, DepoCyt is approved only for lymphomatous meningitis but is often used off label for solid tumor-related LM.

In solid tumor-related LM, a randomized trial comparing intra-CSF liposomal ara-C to MTX found that liposomal ara-C increased median time to neurologic progression (58 vs. 30 days, $P = 0.0068$) but did not affect median survival (105 vs. 78 days, not significant) [Table 6].^[115] The improvement in neurologic PFS with DepoCyt administration was associated with a slight increase in toxicity and decreased patient visits to the hospital (75% reduction).^[78] The liposomal ara-C regimen provided greater quality-adjusted survival regardless of the quality of life valuations placed on time with toxicity and time following disease progression (range, 44-79 days).

Liposomal ara-C has shown similar rate (28%) of response compared with other intra-CSF drugs in nonrandomized series.^[150] In previous studies, the main side-effect of liposomal ara-C was arachnoiditis (i.e., a sterile chemical meningitis) whose incidence was reduced by concomitant administration of oral dexamethasone (4 mg twice daily during 5 days, initiating therapy 1 day before liposomal ara-C injection). Pathologists should be informed of the administration of liposomal ara-C as liposomal particles may be confused microscopically with white blood cells. A randomized phase III trial is currently ongoing in France to evaluate intra-CSF liposomal ara-C (vs. no intra-CSF therapy) in breast cancer-related LM.

Thiotepa

Thiotepa, the only alkylating agent (that by definition has a cell cycle nonspecific mechanism of action) used for intra-CSF chemotherapy, has the shortest half-life (approximately 20 minutes) of all agents used for intra-CSF chemotherapy and shows complete CSF clearance within 4 hours. It is often used as a second-line agent for breast cancer patients who do not respond to or cannot tolerate intra-CSF MTX. Thiotepa unlike other intra-CSF administered drugs rapidly crosses brain capillaries and consequently may result in meaningful systemic serum levels and associated myelosuppression. Because of the short half-life and rapid transcapillary movement, it has been argued that

there is no pharmacological advantage to intra-CSF thiotepa. Nonetheless, the efficacy and toxicity of intra-CSF thiotepa has been prospectively compared with intra-CSF MTX in a randomized trial of adults with LM and demonstrated statistically significant differences in median survival (14 weeks with intra-CSF thiotepa vs. 16 weeks with intra-CSF MTX), a CSF cytological clearance rate of 30% and patients on the thiotepa arm experienced fewer neurological toxicities.^[124] In a retrospective series of 22 breast cancer patients with LM treated second-line with intra-CSF thiotepa (following failure with intra-CSF DepoCyt), the duration of response was 2.8 months (OS: 9.6 months, 1.4-28).^[253]

Combination (multi-agent) intra-CSF chemotherapy

There is no evidence that has demonstrated using an intra-CSF drug combination in LM from solid tumors that shows any superiority to that of a single agent regimen. In addition, increased toxicity and decreased tolerance to treatment has been demonstrated with multi-agent intra-CSF chemotherapy.^[49,145] In the single randomized trial testing this hypothesis, intra-CSF MTX was compared with intra-CSF MTX + ara-C + hydrocortisone in 55 patients.^[145] The combination provided a higher rate of cytological response (38% vs. 14%) and a longer median survival (19 vs. 10 weeks), but a selection bias (better risk patients receiving combination) cannot be excluded.^[162] Another randomized study addressed the question of the potential superiority of a combination of systemic and intra-CSF chemotherapy vs. systemic treatment alone in LM from breast cancer and failed to show a survival advantage for the intra-CSF chemotherapy treated cohort.^[25]

Systemic chemotherapy

In contrast with hematologic neoplasms, the benefit of intra-CSF chemotherapy in LM from solid tumors remains modest. These disappointing results are due to several factors, including intrinsic chemoresistance, limited choice of intra-CSF chemotherapeutic agents, and the poor accessibility of bulky nodules to intra-CSF chemotherapy.^[193] Furthermore, most patients suffering from LM have active systemic disease, which is a main cause of death.^[257] Consequently it is logical to use systemic chemotherapy in an attempt to simultaneously treat systemic disease and LM.^[23,101,120,257] Systemic treatment offers several other advantages such as avoiding the risks of the surgical placement of a ventricular access device, being able to treat patients with a CSF flow block or bulky LM disease as well as having access to a wider range of therapeutic agents.^[113] Some authors have argued that systemic therapy may obviate the need for intra-CSF therapy, a relevant argument that has never been adequately evaluated in a prospective trial of patient with LM.^[20,21,23,101,257]

Siegel reviewed intra-CSF vs. systemic chemotherapy in LM from solid tumors.^[20,21,23,101,120,257,258] The authors concluded that adding intra-CSF chemotherapy to combined radiotherapy and systemic chemotherapy in LM from solid tumors (mainly breast cancers) did not change the overall response rate to treatment, either the median survival or the long-term survival rate, but significantly increased the rate of acute, sub-acute, and delayed neurotoxicity. Conversely, systemic treatment is not always useful since another prospective study in LM in nonsmall-cell lung cancer (NSCLC) patients found that adding systemic chemotherapy to combined radiotherapy and intra-CSF chemotherapy did not improve survival, a possible consequence of the low chemosensitivity of that type of cancer.^[49]

The choice of the most appropriate systemic chemotherapy should be based not only on the chemosensitivity profile of the primary tumor and potential of secondary (acquired) resistance but also upon the ability of drug to achieve effective concentrations in the CSF, features that reflect the chemical properties (lipophilic, low protein-binding, low molecular weight agents) of the systemic agent. Alternatively, high-dose systemic chemotherapy (e.g., MTX) has been administered and shown to be effective for lymphoma and breast cancer-related LM.^[113] It is possible to achieve therapeutic intra-CSF levels with high-dose intravenous MTX (higher than 3 g/m²) or ara-C (e.g., 3 g/m² every 12 h).^[92,198] Myelosuppression is the dose-limiting factor of these treatment schedules.^[263] Unfortunately, the use of these agents through a systemic route remains limited by their narrow spectrum of activity in most solid tumors.

Temozolomide, an alkylating chemotherapy that crosses the blood–brain barrier has been recently evaluated in a phase II trial in first line treatment of LM secondary to breast cancer and NSCLC.^[247] Temozolomide was administered according to a 1 week on/1 week off schedule in 19 patients. Only three patients had clinical benefit, median survival was 43 days (95% CI 28.7-57.3), and median time to progression (TTP) was 28 days (95% CI 14-42). These disappointing results were probably related to the absence of efficacy of temozolomide in these types of cancer.

High-dose methotrexate

High-dose IV methotrexate (HD IV MTX) with leucovorin rescue is an alternative to intra-CSF treatment. It has been prescribed up to 8 g/m², and its efficacy in this indication has been evaluated in small retrospective studies.^[113,223] Cytotoxic CSF MTX levels were achieved, even with lower doses (700 mg/m² initially, followed by a 2800 mg/m² 23-hour continuous infusion), but cytological clearing of malignant cells were variable according to the different schedules (80% vs. 0% in the “8 g/m²” vs. “lower dose” regimens, respectively).

High-dose cytarabine

Therapeutic CSF levels can be achieved by administering ara-C 3 g/m² every 12 hours^[103] or by continuous infusion >4 g/m²/72 hours. However, these schedules are associated with significant toxicity and have not proven beneficial in the treatment of LM from solid tumors.

NEW THERAPEUTIC APPROACHES

Investigational intra-CSF therapies

Innovative intra-CSF chemotherapy regimens

Considerable effort has been invested in evaluating new intra-CSF chemotherapeutic drugs such as diaziquone (AZQ),^[11] mafosfamide,^[14] nimustine hydrochloride (ACNU),^[178] 4-hydroperoxycyclophosphamide (4-HC), 6-mercaptopurine (6-MP),^[1,7,184,271,295] dacarbazine,^[65] and gemcitabine.^[67] Unfortunately, none of these agents has shown clear evidence of activity in LM.

In addition to DepoCyt, intra-CSF administration of MTX encapsulated in liposomes is being developed, but careful evaluation of the potential toxicity of liposomal MTX will be needed. Intra-CSF instillation of a microcrystalline preparation of busulfan (Spartaject) has been studied in clinical trials though again with limited clinical efficacy aside from chronic myelogenous leukemia-related LM.^[77,132] A microcrystalline formulation of temozolomide has also been developed and tested for intra-CSF use in preclinical models of LM.

Intra-CSF etoposide has been evaluated in two feasibility studies and one phase II study.^[57,102,262] In the phase II trial, induction treatment consisted in 0.5 mg etoposide every day given 5 days per week every other week for 8 weeks. Twenty-seven adult patients were enrolled among whom 26% had a cytological response and either stable or improved neurologic status at the end of induction. In responding patients, time to neurologic progression ranged from 8 to 40 weeks (median, 20 weeks). The 6-month neurologic disease PFS was 11%. The modest efficacy in a variety of tumors with varying prognosis makes these studies difficult to interpret.

Topotecan is a topoisomerase I inhibitor that shows antitumor activity against a wide variety of adult and childhood solid tumors. Experimental studies have shown that IVent administration of 1/100th of the systemic dose of topotecan could provide a 450-fold greater CSF exposure. A phase I study of IT topotecan in patients with LM has shown a response in 3 out of 13 children with LM secondary to primary brain tumors.^[16] Arachnoiditis was the dose-limiting toxicity. A phase II nonrandomized study evaluated in 62 patients, the efficacy of IVent topotecan 0.4 mg twice weekly for 6 weeks.^[126] Sixty-five percent of patients completed the 6-week induction period in which 21% had CSF clearance

of malignant cells with a overall median survival of 15 weeks. Chemical meningitis was the most common side effect (32% of patients, 5% grade 3). Topotecan was well tolerated but is unclear if this agent provides any added benefit over other intra-CSF therapies. As noted earlier, several different types of primary tumors were represented (breast, NSCLC, CNS, other), again making the interpretation of results difficult to interpret due to the differing prognosis in this heterogeneous population. Because of its good tolerance profile, combining IVent topotecan with other IVent agents or systemic therapies may be an alternative option to evaluate.

Biological modifiers

Transduction inhibitors,^[6,13,34,76] agents targeting angiogenesis (angiostatin)^[232] or vascular cell adhesion molecules^[29] are currently under investigation.

Intra-CSF IL-2 has been evaluated in patients with LM secondary to melanoma.^[140,196,243] As previously reported with systemic treatment, some patients manifested a long duration of response but side-effects of treatment were not negligible. In a phase II study of 22 patients with LM from various solid tumor cancers, alpha interferon showed a modest activity (median duration of response: 16 weeks, range 8-40), with a transient chemical arachnoiditis and chronic fatigue in the majority of patients.^[53]

Monoclonal antibodies

General comments

A major challenge with biological response modifiers for use in patients with LM, is the poor CSF penetration after systemic administration as illustrated by trastuzumab (humanized monoclonal antibody targeting HER2/neu) and SU5416 (inhibitor of the tyrosine kinase activity of the VEGF receptor).^[175,234,235]

Clinical trials using I^[131] coupled to monoclonal antibodies against tumor antigens directly injected into the CSF have been performed in solid tumors including melanoma, ovarian, and breast primaries with rare occasional long-term clinical responses (7-26 months).^[34,75,144,159,172,201-203] The limits of this approach include the difficulty in creating specific monoclonal antibodies directed against an individual tumor, a limited effect on tumor cells at distance from the tumor cell/monoclonal antibody, and the associated systemic toxicity of the released radiolabeled compound. Intra-CSF immunotoxins, coupling monoclonal antibodies, or biological ligands, such as epidermal growth factor or transferrin to a protein biotoxin have been studied in preclinical models and in a pilot study including eight patients.^[134,154,203,297,301] A greater than 50% reduction of tumor cell counts in the lumbar CSF was observed in four patients, but seven of eight progressed. Side-effects were transient and manageable with steroids and CSF drainage.^[173]

Trastuzumab

LM remain relatively rare (3-5%) in the HER 2/neu positive breast cancer patients as compared with parenchymal brain metastases (approximately 30%).^[9,180,204] In LM, a high level of concordance in the tumor HER 2/neu status has been reported between primary tumors and malignant cells in the CSF unlike the situation in parenchymal brain metastasis.^[217] Trastuzumab CSF/serum ratios have been reported prior to and after WBRT completion and vary from 0.0023 to 0.013 mg/dL and up to 0.02 mg/dL in patients with LM.^[221,266,267] These pharmacological studies suggest very limited entrance of trastuzumab into the CNS regardless of the presence or absence of CNS metastasis or application of WBRT.

A toxicology study with weekly intra-CSF administration of trastuzumab was performed in monkeys with a good tolerance profile at CSF concentrations that exceeded those reported in patients after systemic administration.^[30]

Intra-CSF trastuzumab has been administered at varying doses (5-100 mg) with clinical and cytological success reported in case studies of patients with LM and HER-2/neu positive breast cancer.^[147,175,195,210,224,266,268] Additionally occasional prolonged survival have been reported (>72 months). A complete response (necropsy) has been achieved in a single patient who survived 27 months after LM diagnosis and received 67 cycles of weekly 25 mg IT trastuzumab with marked clinical improvement.^[210]

Intra-CSF trastuzumab has also been administered to two patients in association with intra-CSF MTX and ara-C.^[192] Both patients achieved good control of LM for 13.5 and 6 months without significant toxicity. Intra-CSF trastuzumab has also been prescribed with intra-CSF thiotepa after a first progression following single agent intra-CSF trastuzumab.^[99] This drug combination was chosen based on previous preclinical studies that showed a significant synergism between these two agents.^[220] A clinical benefit was seen in this case report as reflected in a maintained Eastern Cooperative Oncology Group- performance status (ECOG-PS) status of 0 over 24 months. These results are encouraging but the intra-CSF use of trastuzumab remains investigational, as more data and experience are necessary before this regimen can be considered standard. Attempts to develop intra-CSF use of trastuzumab in phase I/II studies are ongoing in France and in the US with NCT01325207 (US) Phase I/II Dose Escalation Trial to Assess Safety of Intrathecal Trastuzumab for the Treatment of Leptomeningeal Metastases in HER2 Positive Breast Cancer and NCT01373710 (France) Phase 1-2 Study of Safety and Efficacy of Intrathecal Trastuzumab Administration in Metastatic HER2 Positive Breast Cancer Patients Developing Carcinomatous Meningitis.

Investigational systemic treatment

Breast cancer

Capecitabine

Capecitabine, an oral prodrug of 5-fluorouracil, has induced encouraging long-lasting responses and stabilization in a limited number of patients with LM from breast cancer but the role in patients with LM is uncertain given the paucity of patients reported to date.^[95,110,237,252,275]

Hormonal treatment

Similar to capecitabine, hormonal agents such as tamoxifen, letrozole, anastrozole, and megestrol have occasionally been useful in breast cancer LM but like capecitabine these reports are usually comprised of a single patient and it is difficult to draw any conclusions as to effectiveness of either hormonal agents or capecitabine in breast cancer-related LM.^[24,52,215]

Nonsmall cell lung cancer

Chemotherapy

Previous reports that suggest systemic chemotherapy improves survival for patients with LM have primarily been of chemoresponsive cancers, such as breast cancer or hematologic malignancies. Recently, Park reported that administration of systemic chemotherapy after diagnosis of LM in NSCLC patients was a significant prognostic factor.^[218] In their retrospective series, 22 patients (44%) underwent systemic chemotherapy (cytotoxic chemotherapy or EGFR inhibitor) after being diagnosed with LM. Patients treated with combined therapy had a prolonged survival (11.5 vs. 1.4 months, $P < 0.001$) such that the authors concluded that a proportion of NSCLC patients with LM may benefit from further systemic chemotherapy. Among those who might be good candidates for aggressive LM-directed treatment, patients with a good ECOG-PS and patients with LM at the time of initial NSCLC diagnosis appear to represent the most favorable subpopulation.

Targeted therapies/epidermal growth factor inhibitors

The epidermal growth factor (EGFR) TKI erlotinib and gefitinib show activity in NSCLC, especially in women, nonsmokers, patients of Asian ethnicity, those with adenocarcinoma, and patients with specific activating mutations of the EGFR.

Several studies have suggested that a subset of patients with LM secondary to NSCLC may benefit with long lasting remission (11-12 months) from erlotinib and gefitinib at normal or higher dose if an EGFR mutation is present.^[72,138,149,155,199,242,264,278,296]

Two recent and a large retrospective series have demonstrated particularly encouraging results with the use of these agents. In the US series, the median survival of the nine patients with LM and known EGFR mutations (all of whom received TKI at some point) was 14 months (range, 1-28 months).^[199] In the Korean series, 14 patients (28%)

with LM received an EGFR TKI with a median survival of 19.2 months.^[218] Thirteen of these 14 patients were never-smokers with adenocarcinoma. EGFR mutation data was available in 16 patients of the Korean series, and of the 11 EGFR mutant patients, the median OS of 6 patients who received EGFR TKI after being diagnosed with LM has not been reached, compared with 1.7 months in 5 patients who did not receive EGFR TKI.

Whether erlotinib should be prescribed in LM at standard dose or high-dose is not clear.^[72,87] Some authors report the pharmacokinetic and therapeutic advantage of a high-dose intermittent pulsatile schedule of EGFR inhibitor (1000-1500 mg/week) in patients with LM.^[72,122] Since a high incidence of recurrence in the CNS has been reported in patients with NSCLC after response to gefitinib, and it has been hypothesized that it might be attributed to incomplete CNS penetration of gefitinib,^[149,212,296] a situation in which high-dose gefitinib has also been evaluated.^[129,149]

Long-lasting meningeal responses have been reported with erlotinib after a prior progression under gefitinib, and vice versa.^[69,139,158,191,218,278,280]

In conclusion, among new generation chemotherapeutic agents, EGFR TKI may be a valuable option in patients with LM particularly in patients with activating EGFR mutations or favorable clinical factors for EGFR TKI responsiveness.

Bevacizumab

CSF levels and CSF/serum indices of (VEGF) have been measured in several studies and were significantly higher in patients with LM, supporting the hypothesis that angiogenesis contributes to LM. VEGF was also negatively correlated with survival in these patients.^[125,233,284]

Bevacizumab is a monoclonal antibody targeting the VEGF ligand. This angiogenic inhibitor is widely prescribed in metastatic colorectal cancer and NSCLC. Retrospective data suggests that bevacizumab is safe in CNS metastases and not associated with an increased risk of intratumoral or intracranial hemorrhage particularly when intracranial lesions are asymptomatic and are of comparatively small volume.^[12] Prospective studies in LM are ongoing to confirm a benefit in the use of anti-VEGF directed therapy.

Intra-CSF bevacizumab is currently being evaluated in LM.^[85,130] A pilot study ($n = 15$) showed that bevacizumab significantly decreases CSF VEGF levels over time and resulted in clinical, imaging and CSF responses or stable disease in 54-73% of LM patients.^[131] Intra-CSF bevacizumab has as well been evaluated in a preclinical rabbit model of LM.^[31]

Melanoma

Patients with LM from melanoma have a poor prognosis, with a median survival less than 2 months.^[43] Intra-CSF

chemotherapy may delay the progression of neurologic signs and symptoms, but benefits are limited and systemic chemotherapy (temozolomide, dacarbazine *DTIC), fotemustine) have generally had only limited efficacy.

Clinical results from the development of immunotherapy agents such as the anti-CTLA4 monoclonal antibody ipilimumab and targeted therapies targeting mutated BRAF such as vemurafenib and dabrafenib suggest that these agents may play a role in the multidisciplinary management of melanoma patients with parenchymal

brain metastases.^[93,98,189,236,292] Leptomeningeal involvement may also be addressed with these new therapies as illustrated by case reports of treating melanoma-related LM with ipilimumab and dabrafenib.^[26,260]

TOXICITY AND COMPLICATIONS OF LM-DIRECTED TREATMENT

Most series of patients treated for LM describe a global complication rate of 70% (all grades of toxicity) with severe complications in 15-20% of

Table 8: Neurologic toxicities and complications of treatments for LM

Nature	Timing	Agents	Clinical and radiological findings	Pathological findings	Treatment and Course
Aseptic meningitis	Several hours after injection	Any IT agent	Mimics bacterial meningitis CSF: Pleocytosis, ↑protein		Oral antipyretics, Antiemetics and steroids Reversible within 1-3 days Further treatment possible Usually totally reversible
Acute encephalopathy	Within 24-48 h after treatment	IT MTX or AraC, IV HD MTX	Seizures, confusion, disorientation and lethargy		
Myelopathy	Within 48 h to months	IT MTX, AraC, L-AraC Thiotepa	Myelopathy CSF: ↑protein MR: Spinal cord swelling, ↑T2WI signal	demyelination	Poor prognosis with persistent paraparesis (60%)
Acute cerebellar syndrome	2-5 days after treatment	HD IV AraC (>3 g/m ²)	Encephalopathy immediately followed by cerebellar syndrome MR: Cerebellar atrophy, reversible and diffuse leukoencephalopathy	Diffuse loss of Purkinje cells +/-WM demyelination	Further treatment possible Recovery after treatment discontinuation, But may be permanent
Acute/subacute encephalopathy	Within 48-72 h/5-6 days after treatment	IT MTX/HD IV MTX	Stroke-like syndrome Normal CSF and Restricted diffusion on MR		Folinic acid/steroids, Reversible within 48-72 h, MR normalization may take up to 4 weeks
Other: Seizures, encephalopathy, myelopathy, radiculopathy, visual loss, communicating hydrocephalus, pseudo-tumor cerebri like syndrome, conus medullaris/cauda equine syndrome, ↓VA		Typically combined RT+HD IV/and IT MTX, or LAra-C			May recover partially or remain permanent
Posterior reversible encephalopathy syndrome	Within 48-72 h	IT MTX	Headache, change in mental status and seizures. MR: Reversible cortical and subcortical changes consisting of high-intensity lesions on T2-WI and FLAIR sequences with postGd ↑, ↓signal intensity on diffusion-WI and ↑ apparent diffusion coefficient	Not fully understood, vasogenic edema in areas of the brain supplied by the posterior circulation	Total resolution within days following causal agent withdrawal
Delayed leucoencephalopathy	Months to years after treatment	High risk if cumulative dose IT MTX > 140 mg Typically combined RT+HD IV/IT CT	Subcortical-frontal syndrome Mutism-akinetism CSF: ↑protein MR: Cortical atrophy, diffuse WM ↑T2WI and FLAIR signal, ventricular dilatation	Disseminated foci of demyelination, axonal loss Necrotizing lesions	No treatment Not reversible

CSF: Cerebrospinal fluid, CT: Chemotherapy, ↓: Decreased, ↑: Elevated, FLAIR: Fluid attenuation inversion recovery, Gd: Gadolinium, H: Hours, HD: High doses, IT: Intrathecal, IV: Intravenous, L: Liposomal, MR: Magnetic resonance, MTX: Methotrexate, RT: Radiotherapy, T2WI: T2 weighted-images, VA: Visual acuity, WM: White matter

cases, and treatment-related deaths in less than 5% of patients.^[2,5,21,25,47,63,88,105,113,114,133,143,148,209,214,238,277,282,291]

Neurological complications are classified according to their time of occurrence (acute, sub-acute, and delayed) and ascribed to the type of treatment (IT or systemic chemotherapy) as illustrated in Table 8.

It remains challenging to differentiate neurologic side-effects secondary to LM-directed treatment from underlying disease progression and from other associated co-morbidities. Elements of prior or concurrent treatment (whole brain radiotherapy, intra-CSF chemotherapy, HD MTX, or HD ara-C) appear to increase intra-CSF drug (MTX and liposomal ara-C) toxicities, regardless of the route (lumbar or ventricular) of administration.^[63]

CONCLUSION

The incidence of CNS metastasis including LM likely will continue to increase in the future due to an improvement of OS of the patients with cancer that is reflective of more effective systemic treatments often with limited penetration into the CNS. Consequently an early diagnosis based upon clinical suspicion is needed to improve the quality of life and the OS of the patients with LM as once neurologic deficits are established rarely reverse with treatment. Available diagnostic tools for LM (CSF cytology and neuraxis imaging) lack both specificity and sensitivity, but new methods of CSF biomarkers are being actively evaluated. Nonetheless prognosis of LM remains poor with a median OS of 3 months and less than 15% of all patients surviving 1 year following diagnosis. At present, LM is treated with combined modality therapy often using some combination of systemic chemotherapy, CNS directed radiotherapy and intra-CSF chemotherapy. Novel targeted agents increasingly are being studied in the treatment of LM and may prove promising in the future. New clinical trials of LM based on a tumor-specific histology are needed to establish the role of these new approaches. Equally important in the management of LM is establishing a common method of assessing response to LM-directed treatment that would improve new trial design and enable cross trial comparisons.

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