Review Article

Leptomeningeal Metastasis From Systemic Cancer: Review and Update on Management

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Leptomeningeal metastasis is an uncommon and typically late complication of cancer with a poor prognosis and limited treatment options. Diagnosis is often challenging, with nonspecific presenting symptoms ranging from headache and confusion to focal neurologic deficits, such as cranial nerve palsies. Standard diagnostic evaluation involves a neurologic examination, magnetic resonance imaging of the brain and spine with gadolinium, and cytologic evaluation of the cerebral spinal fluid. Therapy entails a multimodal approach focused on palliation with surgery, radiation, and/or chemotherapy, which may be administered systemically or directly into the cerebral spinal fluid. Limited trial data exist to guide treatment, and current regimens are based primarily on expert opinion. Although newer targeted and immunotherapeutic agents are under investigation and have shown promise, an improved understanding of the biology of leptomeningeal metastasis and treatment resistance as well as additional randomized controlled studies are needed to guide the optimal treatment of this devastating disease. ***Cancer*** **2018;124:21-35.** © *2017 American Cancer Society.*

KEYWORDS: brain metastasis, carcinomatous meningitis, leptomeningeal carcinomatosis, leptomeningeal disease, leptomeningeal metastasis.

INTRODUCTION

The incidence of leptomeningeal metastasis (LM), also known as carcinomatous meningitis or leptomeningeal carcinomatosis, typically varies by primary tumor type, occurring in approximately 5% to 8% of patients with solid tumors and 5% to 15% of patients with hematologic malignancies.[1] Although it can also be identified in hematologic malignancies and primary brain tumors, such as gliomas, medulloblastomas, and ependymomas, this review will focus on involvement of the subarachnoid space and leptomeninges (arachnoid and pia mater) by solid tumors. Dural involvement can also occur; however, because the dura is not protected by the blood-brain barrier (BBB), treatment is not subject to the same limitations as leptomeningeal involvement and falls outside the scope of this review. Nonetheless, it is important to note that leptomeningeal involvement is often identified concurrently with parenchymal or dural disease. LM usually confers a poor prognosis, with an average survival of 2 to 4 months despite treatment, although response to treatment can vary, with some patients surviving significantly longer.[1] Although treatment options remain limited, advances in the molecular and genetic understanding of systemic malignancies have yielded new opportunities for clinically effective therapies and better tools to predict therapeutic response.

PATHOGENESIS AND EPIDEMIOLOGY

Unfortunately, understanding of disease pathogenesis has not improved markedly since LM was initially described in the late 19th century.[2] Recent studies have started to shed light on the pathogenesis, however, with 1 study demonstrating that cancer cells within the cerebrospinal fluid (CSF) upregulate the production of complement component 3.[3] This, in turn, leads to disruption of the BBB and entry of plasma growth factors into the CSF, promoting cancer cell growth. Cancerous involvement of the leptomeninges is thought to occur by several mechanisms, including direct extension from brain parenchyma, dura, or bone; hematologic spread, particularly through venous plexi and/or perineural extension. LM involvement most commonly occurs in the basal cisterns of the brain, posterior fossa, and cauda equina.[4,5] Invasion of the leptomeninges can lead to local inflammation and impaired CSF resorption, which can then obstruct CSF flow and cause hydrocephalus and/or increased intracranial pressure.

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DOI: 10.1002/cncr.30911, **Received:** April 26, 2017; **Revised:** June 27, 2017; **Accepted:** July 6, 2017, **Published online** November 22, 2017 in Wiley Online Library (wileyonlinelibrary.com)

TABLE 1. Signs and Symptoms of Leptomeningeal Metastasis

Brain
Headache
Confusion
Nausea/vomiting
Cranial nerve palsies
Vision changes (particularly double vision)
Tinnitus, decreased hearing
Facial numbness, weakness
Dysarthria
Dysphagia
Seizure
Ataxia
Cognitive impairment
Spine
Bowel/bladder dysfunction
Pain (neck, back, or radicular)
Paresthesias
Focal weakness
Nucal rigidity
Hyporeflexia
Clinical syndromes
Multiple cranial neuropathies
Syndrome of inappropriate diuretic hormone secretion (SIADH)
Rapidly progressive dementia

TABLE 2. Differential Diagnoses

Infectious meningitis
Chemical meningitis/arachnoiditis (secondary to intrathecal chemotherapy)
Multiple brain metastases
Paraneoplastic syndrome
Limbic encephalitis
Encephalomyelitis
Paraneoplastic cerebellar degeneration
Intracranial hypotension (secondary to lumbar puncture)
Toxic metabolic encephalopathy
Metabolic or chemotherapy-induced neuropathy
Steroid myopathy
Cord compression

Although nearly every systemic tumor has been reported to metastasize to the leptomeninges, common solid tumors include lung, breast, and melanoma. Incidence varies by tumor type and ranges from 5% to 8% of metastatic breast cancers,[6] from 9% to 25% of lung cancers (greater in small cell lung cancer),[7] and from 6% to 18% of melanomas.[8] Overall, the incidence of LM may be increasing in the setting of improved systemic control and treatments that poorly penetrate the BBB, leading to longer survival and a reservoir of tumor cells in the central nervous system (CNS).[9-13] Progressive systemic disease is also observed in 60% to 70% of patients at the time of LM diagnosis.[14,15] In a large case series of 187 patients, including 150 patients with solid malignancies (primarily breast and lung cancers), 58% had concurrent or prior parenchymal brain involvement.[16] The median time from systemic cancer diagnosis to the diagnosis of LM ranges from 1.2 to 2.0 years in solid tumors and averages 11 months in hematologic malignancies.[14,16,17]

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Signs and symptoms of LM depend on the location of involvement. Given the frequent multifocality, clinical presentation may be nonspecific, and the index of suspicion must be high. Common clinical findings are often attributable to cranial and spinal nerve dysfunction, increased intracranial pressure (ICP), or meningeal irritation (Table 1). Cranial nerves VI, VII, and VIII are commonly affected, leading to diplopia, facial weakness, and changes in hearing, respectively. Spinal signs include dermatomal sensory loss, radicular pain, bowel and bladder dysfunction, and limb weakness. Other general symptoms include headache, nausea, vomiting, and changes in mental status. Involvement or compression of small vessels in the subarachnoid space may also lead to ischemic infarct.

Given the broad presenting features and frequently complex treatment histories, consideration should also be given to alternative diagnoses, including chronic infectious meningitis, autoimmune disorders (eg, sarcoidosis), meningeal reaction to brain abscess, side effects of chemotherapy or radiation, paraneoplastic syndromes, and toxic-metabolic encephalopathy (Table 2). In immunocompromised cancer patients, causes of infectious meningitis or encephalitis include bacterial (eg, tuberculosis, listeriosis), fungal (eg, C*ryptococcus*, candidiasis), or viral (eg, cytomegalovirus, varicella zoster virus, Epstein-Barr virus, herpes simplex virus, and JC virus).[18]

DIAGNOSTIC EVALUATION

The diagnosis of LM remains challenging, with no test sufficiently sensitive to rule out involvement. Magnetic resonance imaging (MRI) of the brain and spine is recommended if there is clinical suspicion and may reveal leptomeningeal enhancement, which is often irregular and nodular (Fig. 1).[19] Subependymal deposits and hydrocephalus may also be seen. Imaging should be interpreted with caution if a recent lumbar puncture has been performed because resulting low ICP or inflammation may lead to transient enhancement. The sensitivity of MRI with gadolinium is approximately 70%, with specificity of 77% to 100% (higher for solid tumors than for hematologic malignancies).[20-22] In the presence of typical clinical features, an abnormal MRI is sufficient to make the diagnosis.[22] 111-Indium or 99-technetium ventriculography may be performed to evaluate CSF flow in select

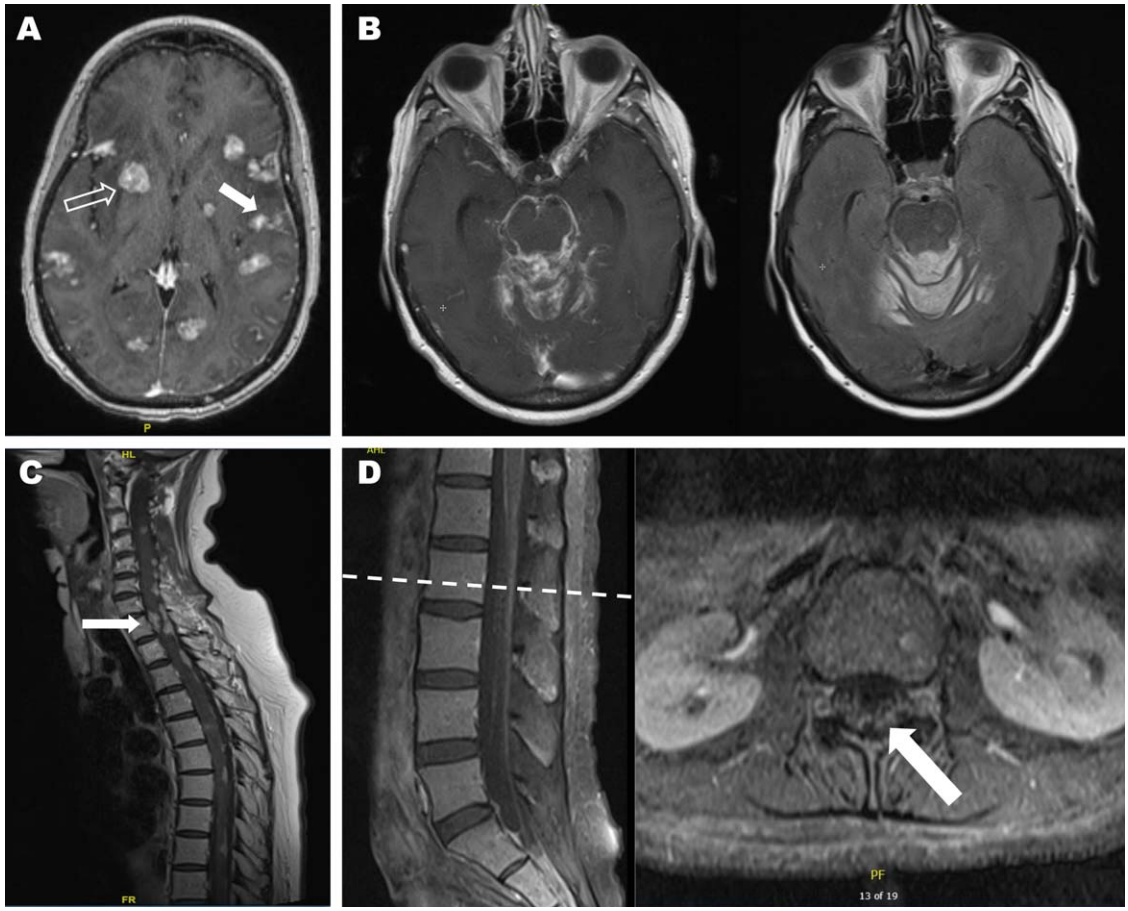

Figure 1. Magnetic resonance imaging (MRI) of leptomeningeal metastasis is illustrated. (A) An axial, T1-weighted, gadolinium-enhanced MRI demonstrates parenchymal metastasis (open arrow) and leptomeningeal metastases (representative lesion denoted by solid arrow) from breast cancer. (B) Axial, T1-weighted, (*left*) gadolinium-enhanced and (*right*) T2/fluid-attenuated inversion recovery (FLAIR) sequences (right) reveal enhancement along the cerebellar folia and surrounding the brainstem with associated sulcal FLAIR hyperintensity representing leptomeningeal metastasis from neuroendocrine carcinoma of the lung. (C) Sagittal cervical and thoracic gadolinium-enhanced MRI reveals nodular leptomeningeal spinal metastases from breast cancer with compression of the cervical cord (solid arrow). (D) T1 gadolinium-enhanced (*left*) sagittal and (*right*) axial sequences show enhancement and clumping of the cauda equina nerve roots (solid arrow).

circumstances when this may help guide treatment, as described below.

If it is safe to perform, then lumbar puncture is recommended (Fig. 2) and often reveals mild pleocytosis with elevated protein and hypoglycorrhachia. In cases of profound hypoglycorrhachia, infectious etiologies (described above) should be considered, particularly bacterial and fungal meningitis. An elevated opening pressure may be observed in 50% to 70% of patients, depending on the extent of leptomeningeal involvement.[23] False-negative cytology results can be minimized in several ways.[17] First, sufficient CSF volume of at least 10 mL should be obtained for cytologic analysis. Second, the CSF specimen should be processed as soon as possible to reduce the risk of cell death. Glantz et al reported a false-negative error rate of 36% in samples that were refrigerated for 48 hours versus samples collected from the same patients that had positive cytology upon immediate processing. Third, obtaining CSF from a site of known leptomeningeal disease may increase the likelihood of detecting abnormal cells, although this may be more relevant in untreated patients who are screened for LM than in those who have received intrathecal (IT) or systemic treatment. Finally, the procedure should be repeated at least once if the initial sample is negative and LM is suspected. CSF cytology is positive in >90% of patients with suspected LM after 3 high-volume lumbar punctures with a specificity of >95%.[15,24] False-positive results may be obtained in infectious or other inflammatory conditions with reactive lymphocytes. Flow cytometry and additional

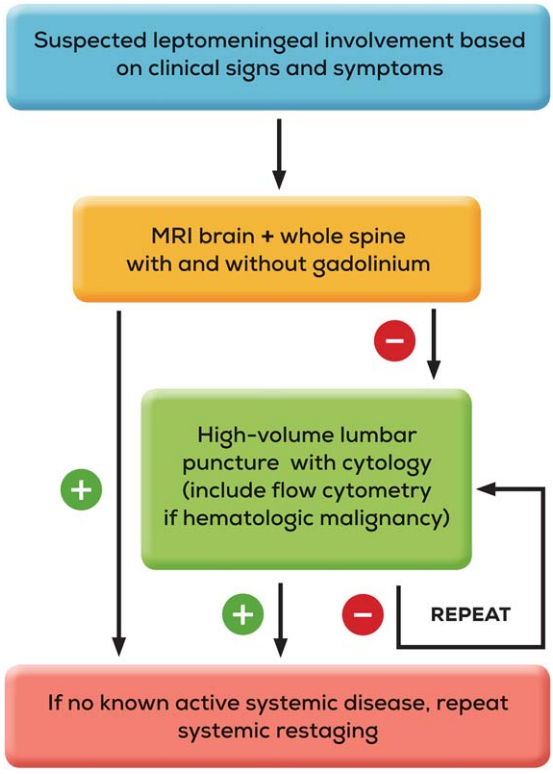

Figure 2. This is a diagnostic algorithm of the current study. MRI indicates magnetic resonance imaging.

molecular studies may be valuable in select clinical scenarios. Flow cytometry has increased sensitivity compared to cytomorphologic analysis in the setting of hematologic malignancies.[25]

The use of CSF tumor markers has been limited by their low sensitivity and specificity as well as significant assay variability. However, these markers may support the diagnosis in the face of an otherwise equivocal diagnostic evaluation. In particular, CSF levels >1% of serum levels of specific tumor markers, such as carcinoembryonic antigen (CEA) from adenocarcinomas, α-fetoprotein from hepatocellular and testicular carcinomas, and β-human chorionic gonadotropin from choriocarcinoma and testicular carcinomas, are relatively specific for CSF involvement.[26,27] These markers may also have value in following response to treatment. More recently, cell-free DNA present in the CSF has been used to detect tumor-specific somatic alterations through next-generation sequencing.[28-30] The detection of tumor-specific mutations may increase the sensitivity and specificity of diagnostic CSF evaluation, aid in the assessment of treatment response, and shed light on mechanisms of CNS resistance to systemic therapy. Finally, if there is no known active, systemic disease, then systemic restaging should be performed as this may guide further treatment.

ASSESSING RESPONSE TO THERAPY

Of the 6 randomized controlled trials (Table 3)[31-36] conducted in LM, most have incorporated neurologic examination and CSF cytology to determine response to treatment. However, assessment of neurologic response was often based on subjective neurologic evaluations, MRI criteria were not used or were not stated, and cytologic evaluation was not uniform.[37] The site of CSF sampling is also important in assessing response because negative cytology at 1 site (eg, through an Ommaya reservoir) does not necessarily define a cytologic response when the initial diagnosis was made based on cytologic evaluation at another site (eg, lumbar puncture). Primary endpoints varied across trials, including overall survival, neurologic response rate, time to neurologic progression, and progression-free survival. Secondary endpoints included neurologic progression, neurologic response rate, safety and toxicity profile, cause of death, Karnofsky performance status (KPS) evolution over time, quality of life, LM-specific survival, and overall survival. Secondary endpoints, such as patient-reported quality of life and neurologic progression, may be important considerations for settings in which disease is often advanced and overall survival is unlikely to be prolonged, but symptom palliation remains a central goal of therapy.

Standardized assessment was only recently proposed by the Response Assessment in Neuro-Oncology (RANO) Group in 2016 after recognition of the limitations in assessing outcomes.[38] The proposed criteria include a standard neurologic examination, MRI of the brain and spine, and CSF evaluation. Therapeutic response can only be determined in the setting of a negative cytologic evaluation (as well as flow cytometry in hematologic malignancies), definite improvement in CNS imaging, decreased or absent steroid dose (in hematologic malignancies only), and improved symptoms. It is important to note that definitive worsening of CNS imaging is sufficient to determine progressive or refractory disease. Response based on CSF cytology is considered when cytology converts from positive to negative at all sites that were previously positive and is subsequently confirmed after 1 month. Of note, there was a lack of consensus regarding response determination in a patient with persistently positive cytology in the setting of stable or improved clinical and radiographic status. Although suggested, the criteria do not include patient-reported outcomes, such as the MD Anderson Cancer Center Symptom Inventory Brain Tumor Module (MDASI-BT), the MD

TABLE 3. Randomized Controlled Trials in Leptomeningeal Metastasis[31-36,41]

Trial	No. of Patients	Tumor Type	Treatment Arms	Endpoint	Significance
Hitchins 1987[31]	44	SCLC, 29%; breast, 25%; primary brain, 9%; NSCLC, 7%; lymphoma, 7%	IT MTX	RR, 61%; OS, 12 wk	RR, $P > .10$; OS, $P = .084$
			IT MTX + Ara-C	RR, 45%; OS 7 wk	
Grossman 1993[32]	52 (Assessable)	Breast, 48%; lung, 23%; lymphoma, 19%	IT MTX	OS, 15.9 wk; SD, 32%	RR, unknown; OS, $P = .36$
			IT thiotepa	OS, 14.1 wk; SD, 12.5%	
Glantz 1999[33]	28	Lymphoma, 100%	IT DepoCyt	RR, 71%; TTP, 78.5d; OS, 99.5 d	RR, $P = .006$; TTP/OS, $P > .05$
			IT Ara-C	RR, 15%; TTP, 42 d; OS, 63 d	
Glantz 1999[34]	61	Breast, 36%; NSCLC, 10%; primary brain, 23%; melanoma, 8%; SCLC, 7%	IT DepoCyt	RR, 26%; TTP, 58 d; OS, 105 d	RR, $P = .76$; TTP, $P = .007$; OS, $P = .15$
			IT MTX	RR, 20%; TTP, 30 d; OS, 78 d	
Boogerd 2004[35]	35	Breast cancer, 100%	Systemic therapy + RT + IVT MTX	Neurologic improvement/ stabilization, 59%; TTP, 23 wk; OS, 18.3 wk	Neurologic response: unknown; TTP, unknown; OS, $P = .32$
			Systemic therapy + RT	Neurologic improvement/ stabilization, 67%; TTP, 24 wk; OS, 30.3 wk	
Shapiro 2006[36]	128	Solid tumors, 80%; lymphoma, 20%	Combined IT DepoCyt (solid tumor and lymphoma)	PFS, 35 d	PFS, $P = .7321$; HR, 0.98
			Combined IT MTX (solid tumor) + IT Ara-C (lymphoma)	PFS, 43 d	
			IT DepoCyt (lymphoma)	PFS, 34 d; cytologic response, 33.3%	PFS: HR, 0.12; cytologic response, $P = .3640$
			IT Ara-C (lymphoma)	PFS, 50 d; cytologic response, 16.7%	

Abbreviations: Ara-C, cytarabine; d, days; DepoCyt, liposomal cytarabine; IT, intrathecal chemotherapy; IVT, intraventricular; MTX, methotrexate; NSCLC, non-small cell lung cancer; OS, median overall survival; PFS, progression free survival; RR, response rate; RT radiotherapy; SCLC, small cell lung cancer; TTP, time to progression; wks, weeks.

Anderson Cancer Center Symptom Inventory Spine Tumor Module (MDASI-SP), or the Functional Assessment of Cancer Therapy-Brain. These experts acknowledge that the proposed criteria to standardize LM response assessment require validation and refinement; however, the criteria serve as a new standard that can be incorporated into future clinical trials to enable better comparisons across trials and more rigorous assessment of therapeutic response.

PROGNOSIS

Despite advances in care, the prognosis for patients with LM remains poor, with an overall survival of approximately 2 to 4 months from the time of diagnosis if treated.[1] Untreated, death occurs from progressive neurologic deterioration in 4 to 6 weeks.[15] A KPS > 70, chemosensitivity of primary cancer, unimpaired CSF flow, CSF protein levels <50 mg/dL, and active treatment have been identified as favorable prognostic factors.[39,40] One study of patients who had solid and hematologic malignancies and cytologically confirmed LM demonstrated that those with a KPS ≥ 70 had a median survival of 15.5 weeks compared with 6 weeks in those with a KPS <70.[40] The US National Comprehensive Cancer Network (NCCN) identifies poor prognostic factors as a KPS <60, severe neurologic deficits, extensive systemic disease with few treatment options, bulky CNS disease, and encephalopathy.[41] Primary tumor type also plays an important role. In 1 patient series, those with hematologic

malignancies had slightly improved survival of 4.7 months compared with 2.3 months for those with solid tumors.[16] Within solid tumors, breast cancer LM has a superior prognosis compared to other tumor types, with a median survival of 5 to 7 months.[16,42-45]

TREATMENT

The treatment of LM has traditionally been directed toward palliation, although new therapies have produced promising response rates. While systemic chemotherapies have been limited in their ability to cross the BBB, they are often combined with radiation and other palliative surgical interventions with the goal of preventing neurologic deterioration, maintaining quality of life, and prolonging survival. IT chemotherapy is frequently considered; however, clinical trial data are limited. Because of the paucity of prospective, randomized trials, optimum therapy is poorly defined, and treatment is mostly guided by expert opinion.

Radiation

Radiation is typically geared toward symptom management and thus often targets bulky, symptomatic sites of disease, particularly in the spine. Frequently, whole-brain radiotherapy at doses between 30 to 40 grays (Gy) in 2-Gy to 3-Gy fractions is administered, although an abbreviated course of 20 Gy in 4-Gy fractions is sometimes considered in patients with a poor prognosis or who are less likely to tolerate treatment.[26,46] Radiation may also restore CSF flow and relieve hydrocephalus by reducing tumor bulk and, in doing so, facilitate the use of IT chemotherapy.[47] In addition to the long-term side effects of radiotherapy alone, there may also be an increased risk of late leukoencephalopathy when combined with other chemotherapeutic agents, such as intravenous or IT methotrexate.[35,48-52] Radiation is unlikely to prolong survival based on retrospective studies in patients with breast and lung cancers, but it can result in rapid symptom improvement.[53,54] Eradication of tumor cells from the leptomeninges would require craniospinal irradiation, which carries significant potential CNS and systemic toxicities, including myelosuppression, that may compromise future cytotoxic chemotherapy options. In addition, it is often considered impractical in the setting of a poor overall prognosis. Although it is not standard practice, craniospinal irradiation may be used in the setting of LM from hematologic malignancies because these are frequently highly radiosensitive.[50,55,56]

IT Chemotherapy

Although IT delivery of chemotherapy bypasses the BBB and minimizes systemic side effects, it is not without limitations. Agents can be administered by lumbar puncture or through surgical placement of a reservoir that directly feeds into the ventricular system through a catheter (such as an Ommaya reservoir). Commonly used agents include methotrexate (a folate antagonist), thiotepa (an alkylating agent), cytarabine (a pyrimidine analog), and sustained-release liposomal cytarabine (DepoCyt; Pacira Pharmaceuticals, Inc, San Diego, California). Several retrospective studies have demonstrated a survival benefit from IT therapy.[45,47] Of the 6 randomized clinical trials conducted in LM, all focused on IT therapy (Table 3). It is important to note that most trials and series excluded patients who were deemed too sick for treatment, which may constitute a significant proportion of patients at presentation. The study by Boogerd et al[35] was the only trial to compare IT chemotherapy with standard therapy without IT treatment. In 35 patients who had breast cancer, with 17 randomized to receive IT chemotherapy, there was no difference in survival or neurologic response, and the trial was closed prematurely because of low accrual. Another retrospective study of 104 patients with LM from any solid tumor who received systemic therapy and radiation with or without IT therapy also demonstrated no difference in median survival.[51] Quality-of-life measures were not assessed in either study, and both studies reported increased rates of treatment-related neurotoxicity in patients who received IT chemotherapy. A study of liposomal cytarabine in breast cancer LM is currently underway (clinicaltrials.gov identifier NCT01645839).

Aseptic or chemical meningitis is one of the more common complications observed in up to 43% of patients and characterized by sterile CSF pleocytosis as well as clinical signs and symptoms of meningitis.[57,58] Although Chamberlain et al observed that the frequency of this complication was independent of the type of IT chemotherapy administered through Ommaya reservoirs (between methotrexate, cytarabine, and thiotepa), because of the frequent occurrence of chemical arachnoiditis with IT liposomal cytarabine, it is now standard to coadminister it with dexamethasone.[57] Corticosteroids and intravenous hydration can be used to treat and mitigate the symptoms of this complication. However, infectious meningitis should be ruled out when aseptic meningitis is considered and is present in 8% to 24% of patients receiving intraventricular therapy.[59] The most common organism is *Staphylococcus epidermidis*, and treatment requires intravenous and intraventricular antibiotics; removal of

the reservoir may be indicated as well.[60,61] Other complications of IT chemotherapy include leukoencephalopathy (particularly when combined with radiation), myelopathy, seizure, and inadvertent subdural or epidural delivery if administered by lumbar puncture. Despite the method of administration, myelosuppression can also be observed in up to 18% of patients.[57]

The site and pattern of involvement are important issues when considering IT chemotherapy. Penetration is limited in areas of bulky leptomeningeal disease, to approximately 2 to 3 mm.[58] If there is evidence of complete or partial obstruction of CSF flow, then excessive build-up of the chemotherapy may lead to neurotoxicity and treatment failure. Radionucleotide flow studies may be helpful to evaluate CSF flow before therapy. However, these studies are more invasive than conventional imaging and are often technically challenging, requiring cisternograms immediately after tracer injection as well as 4 to 6, 24, 48, and sometimes even 72 hours after injection.[62] In the setting of ventriculoperitoneal shunts (VPS), there are also concerns about the accumulation of chemotherapy leading to neurotoxicity should there be shunt malfunction or intraperitoneal toxicity from draining of the IT drug. However, a small retrospective study demonstrated that IT chemotherapy could safely be administered through a reservoir-on/off valve VPS.[63]

Systemic Chemotherapy

Although systemic chemotherapy is limited by the ability of agents to penetrate the BBB, there is breakdown of the BBB in the setting of LM, and it has been demonstrated that several chemotherapies can achieve therapeutic levels in the CSF when administered systemically. In addition, systemic chemotherapy does not depend on CSF flow, is able to penetrate bulky nodular disease, concurrently addresses any systemically active disease, and avoids the potential procedural complications associated with IT therapy. The type of malignancy should guide the choice of systemic chemotherapy. Options include high-dose methotrexate (3-8 g/m)[64,65] high-dose cytarabine (3 g/m)[66,67] capecitebine (particularly for breast cancer),[68-71] thiotepa,[72] and temozolomide.[73] Response has also been reported with high-dose etoposide in 5 patients with LM from small cell lung cancer.[74] Systemic chemotherapy, particularly when combined with radiation, can lead to acute or delayed leukoencephalopathy, subacute encephalopathy, and acute cerebellar syndrome associated with high-dose cytarabine.

Numerous retrospective studies have demonstrated improved survival in patients who received systemic chemotherapy.[42-44,75,76] Some argue that, based on the randomized trial by Boogerd et al[35] and other retrospective studies, IT chemotherapy adds little value to systemic chemotherapy.[35,51,64,77] Conversely, however, a prospective series of patients with LM from nonsmall cell lung cancer (NSCLC) identified no added survival benefit from systemic chemotherapy when combined with radiotherapy and intraventricular chemotherapy.[47] The role of systemic versus IT chemotherapy may vary based on primary tumor type, as the studies that demonstrated little added value from IT therapy primarily consisted of patients with lymphoma or breast cancer.

Targeted Therapies

Melanoma

In subsets of solid tumors, targeted therapies have demonstrated promising results. Approximately 50% of melanomas harbor an activating mutation in the v-Raf murine sarcoma viral oncogene homolog B (BRAF), most commonly BRAF V600E (valine-to-glutamic acid mutation at position 600), which constitutively activates the mitogen-activated protein kinase pathway. In LM from melanoma, there are reports of response to BRAF inhibitors such as vemurafenib[78] and dabrafenib.[79] Most mechanisms of resistance to BRAF inhibition are mediated through mitogen-activated protein kinase kinase (MEK), and 3 randomized phase 3 studies in metastatic melanoma have now demonstrated the superiority of combined BRAF and MEK inhibition compared with BRAF inhibition alone.[80-82] This strategy has not been evaluated in patients with LM involvement to date, although all 3 trials included patients with stable brain metastases.

Breast cancer

Human epidermal growth factor receptor 2 (HER2) is overexpressed in approximately 30% of primary breast cancers and is associated with an increased risk of CNS involvement.[83] Multiple reports describe response to IT trastuzumab, a humanized monoclonal antibody against HER2, in LM from HER2-positive breast cancer.[84-89] Preliminary results from a phase 1 trial of IT trastuzumab in patients with HER2-positive breast cancer and LM demonstrated that it was well tolerated, and several phase 2 trials are ongoing (clinicaltrials.gov identifiers NCT01325207 and NCT01373710).[90] Combination approaches are also being studied, with a phase 1 trial of lapatinib, a small-molecule dual tyrosine kinase inhibitor (TKI) that targets HER2 and EGFR, in combination with capecitabine, an antimetabolite chemotherapeutic, currently underway in HER2-positive patients with LM (clinicaltrials.gov identifier NCT02650752). The phase 2

TABLE 4. Active Therapeutic Clinical Trials for Patients With Leptomeningeal Metastases

NCT	Phase	Primary Histology	Site, Sponsor	Drug	Primary Outcome(s)	Secondary Outcome(s)	Study Arms	Key Inclusion Criteria	Key Exclusion Criteria	Recruiting?
NCT02939300	II	Melanoma	Massachusetts General Hospital, Bristol-Myers Squibb	Nivolumab and ipilimumab	OS	IC/EC RR, LM RR, IC/EC PFS, toxicity	Single arm: Combined nivolumab and ipilimumab followed by nivolumab monotherapy	• Adults only • ECOG ≤2 or KPS ≥60 • Life expectancy ≥3 wk • LM confirmed by cytology	• Active, known, or suspected autoimmune disease • Condition requiring systemic corticosteroid treatment • Prior systemic treatment with anti-CTLA4 antibody • Known history of active TB	Yes
NCT01645839	III	Breast cancer	Multiple sites in France, Oscar Lambret Center	Liposomal cytarabine	Neurologic PFS	Neurologic, physical, cognitive, cytologic, radiologic improvement; PFS (radiologic, clinical, cytologic); OS, toxicity	A: Standard systemic treatment without liposomal cytarabine B: Standard systemic treatment with liposomal cytarabine	• Adult women only • ECOG ≤2 • Life expectancy ≥2 mo • New diagnosis of LM by cytology *or* clinical signs and symptoms • Measurable CNS disease <0.5 cm or >0.5 cm if focused radiation therapy	• Symptomatic BM or BM requiring WBRT • Previous CSI or IT therapy • Previous systemic treatment with ARA-C or high-dose systemic methotrexate • Contraindication to LP and ventricular catheterization • VPS	Yes
NCT01325207	I/II	HER2+ breast cancer	Multiple US sites; Northwestern University	IT trastuzumab	Safety, MTD	Response (radiologic, cytologic, clinical), CSF PK	Single arm, dose escalation: Twice weekly for 2 wk, then weekly for 4 wk, then every 2 wk	• Adults only • HER2+ by IHC or FISH breast cancer • LM determined by MRI or cytology • Life expectancy ≥8 wk • KPS ≥50 • Willing to have Ommaya reservoir placed • May continue on IV trastuzumab, lapatinib, or hormonal agents if controlling ECD and developed LM while on therapy	• Previously-treated BM • BM requiring active treatment • Systemic agents (chemotherapy) that have CNS penetration, unless LM developed while on these agents and ECD controlled	Ongoing, not recruiting
NCT01373710	I/II	HER2+ breast cancer	Multiple sites in France, Curie Institute	IT/IVent trastuzumab	MTD	CNS TTP; QoL; OS; PFS; PK; radiologic, CSF response	Single arm, dose escalation: 1 injection/wk during 8 wk by lumbar puncture or Ommaya reservoir, 4 dose levels expected from 30 to 150 mg	• Adults only • Life expectancy ≥2 mo • HER2+ by IHC and/or FISH • LM diagnosis by cytology and/or clinical signs and symptoms of LM with abnormal MRI	• Symptomatic, untreated BM • Symptomatic BM, unless surgery and/or RT were performed ≥3 wk before treatment initiation and lesion(s) accessible to IT or IVent treatment • Obstructive hydrocephalus • On lapatinib, unless washout >2 wk before first dose of IT study drug • VPS or atrial shunt, unless can be turned off during treatment	Yes
NCT02650752	I	HER2+	3 US sites, Memorial Sloan Kettering Cancer Center	High-dose lapatinib plus capecitabine	MTD	Not specified	Single arm: Weekly treatment cycle consisting of lapatinib 3 d on/11 d off plus capecitabine 7 d on/7 d off; both drugs administered orally with dose escalation	• Adult women only • HER2+ by IHC or FISH • Life expectancy ≥12 wk • ECOG ≤2 • Nonescalating corticosteroid dose (≤16 mg dexamethasone daily) for ≥5 d • Radiologic evidence of new and/or progressive BM/LM or CSF cytologic evidence of LM	• Prior capecitabine therapy allowed if ≥6 mo since last dose • Everolimus therapy • Craniotomy, other major surgery, open biopsy, or significant traumatic injury ≤4 wk of enrollment • HIV infection or chronic hepatitis B or C • Concurrent chemotherapy, hormone therapy, RT, surgery, immunotherapy, tumor embolization, or biologic therapy, except for trastuzumab or hormone therapy	Yes

TABLE 4. *Continued*

NCT	Phase	Primary Histology	Site, Sponsor	Drug	Primary Outcome(s)	Secondary Outcome(s)	Study Arms	Key Inclusion Criteria	Key Exclusion Criteria	Recruiting?
NCT02422641	II	Breast cancer	Wake Forest University and Sidney Kimmel Comprehensive Cancer Center, Wake Forest University Health Sciences	High-dose methotrexate	3-mo OS	1-y OS, PFS, tolerability, cost, cytologic sterilization	Single arm: high-dose methotrexate (8 g/m^2 IV every 2 wk)	• Adults only • ECOG 0-1 • Triple-negative, HER2+, or HR+ hormone-refractory breast cancer • Cytologic or radiographic confirmation of LM with/without BM	• Chemotherapy or SRS within 2 wk, WBRT within 6 mo • Heart failure (NYHA class >3) • Prior treatment with any methotrexate-containing systemic regimen within 1 y (excluding IT methotrexate) • Concurrent or planned systemic chemotherapy, radiotherapy, or new hormone/anti-HER2–directed therapy	Yes
NCT02616393	II	EGFR-mutant NSCLC	Multiple US sites, Kadmon Corp. LLC	Tesevatinib	Clinical activity using RECIST 1.1 (cohorts A and C), symptom resolution (cohort B_	QoL, median PFS, CNS TTP, median OS, PK	Dosing the same among all arms; 300 mg orally once daily • A: NSCLC who have progressed with LM • B: NSCLC who have progressed with BM • C: NSCLC with BM at initial presentation	• Adults only • EGFR mutation that has clinical response to erlotinib, afatinib, or gefitinib • BM occurrence or progression while receiving erlotinib, afatinib, or gefitinib • Measurable BM (≥10 mm) • ECOG ≤2 • No clinically significant progression outside the CNS on most recent EGFR-inhibitor therapy	• First day of dosing with tesevatinib ○ <2 wk from the last treatment of cytotoxic chemotherapy, biologic therapy, or immunotherapy ○ <6 wk for nitrosoureas and mitomycin C ○ <2 wk since surgical procedure ○ <4 wk since last CNS-directed RT ○ <3 d since discontinuing erlotinib, afatinib, or TKI • Any concurrent BM (cohorts A and C), LM (cohort B) therapy other than study treatment	Yes
NCT02336451	II	NSCLC with ALK rearrangement	Multiple US and international sites, Novartis	Ceritinib	ORR	TT(I)R and TTR, IC/EC DOR, IC/EC ORR, IC/EC DCR, PFS, safety, PK	Dosing the same among all arms; 750 mg orally once daily • ALK+ NSCLC with BM, without LM, with previous exposure to crizotinib • ALK+ NSCLC with BM, without LM, without previous exposure to crizotinib • ALK+ NSCLC with LM, with or without previous exposure to crizotinib	• ≥1 Measurable EC lesion • ECOG ≤2 • Life expectancy ≥6 wk	• Prior ALK inhibitor other than crizotinib • BM requiring WBRT • Previously-treated BM, unless progressive or new since WBRT • Unstable or increasing dosage of corticosteroids • Planning to receive local treatment to BM (eg, surgery, SRS, WBRT, IT chemotherapy)	Yes
NCT00445965	II	GD2-positive LMD (primarily neuroblastoma, primary CNS tumors)	Memorial Sloan Kettering Cancer Center, same	IVent ^{131}I-labeled monoclonal antibody 3F8	6-mo OS, RR (alive at 6 mo)	Toxicity	Single arm: 10 mCi injected IT weekly for up to 4 courses as tolerated	• Children and adults • Histologically confirmed diagnosis of a malignancy known to express GD2	• Rapidly progressing or deteriorating neurologic examination • Obstructive or symptomatic communicating hydrocephalus • CSI or systemic chemotherapy <3 wk before start of protocol • >45 Gy CSI or >72 Gy focal brain radiation	Ongoing, not recruiting

TABLE 4. *Continued*

NCT	Phase	Primary Histology	Site, Sponsor	Drug	Primary Outcome(s)	Secondary Outcome(s)	Study Arms	Key Inclusion Criteria	Key Exclusion Criteria	Recruiting?
NCT00089245	I	Malignancy known to be 8H9 reactive, confirmed by IHC or bone marrow IF	Memorial Sloan Kettering Cancer Center, same	^{131}I-labeled 8H9	MTD over 2 y	Not specified	Single arm, dose escalation with patients entering in cohorts of: • Three patients at each dose level from 10-60 mCi • Six patients at each dose level from 70-100 mCi	• Children and adults • LMD refractory to conventional therapies or recurrent brain tumors with predilection for LM dissemination (medulloblastoma, PNET, rhabdoid tumors)	• Rapidly progressing or deteriorating neurologic examination • Obstructive or symptomatic communicating hydrocephalus • CSI or systemic chemotherapy <3 wk before start of protocol	Yes
NCT02308020	II	HR+ breast cancer, NSCLC, or melanoma	Multiple US sites, Eli Lilly and Company	Abemaciclib	IC ORR	BOIR, IC DOR, DCR, IC DCR, ICBR, OS, OR, PFS, PK at 3 mo	Same treatment for all arms, UOS: 200 mg study drug every 12 h on days 1-21 or each 21-d cycle • A: HER2+ breast cancer • B: HER2− breast cancer • C: Surgical resection indicated for intracranial lesions, drug on days 5-14 before surgical resection and resumed dosing after wound healing • D: NSCLC, 150 mg drug if receiving concurrent gemcitabine or pemetrexed • E: Melanoma • F: HR+ breast cancer, NSCLC, or melanoma	• Adults only • KPS ≥70 • Life expectancy ≥12 wk • Completed local therapy (surgical resection, WBRT, or SRS) ≥14 d before initiating study drug	• Require immediate local therapy (including WBRT, SRS, surgical resection) • Concurrent EIAED use • Evidence of symptomatic intracranial hemorrhage • ≥2 Seizures within 4 wk before study initiation	Yes
NCT02886585	II	Multiple histologies	Massachusetts General Hospital, Merck Sharp & Dohme Corp.	Pembrolizumab	ORR, OS, EC ORR	Toxicity, OS rate, IC/EC RR, EC PFS	Same treatment for all arms, UOS: study drug Q 3 wk • A: Previously untreated BM • B: Progressive BM after prior local CNS-directed therapy (e.g. WBRT, SRS, or surgery) • C: LM with positive CSF cytology • D: 1-4 BM from histologically confirmed melanoma with clinical indication for SRS, cycles 1 and 2 of study drug administered 3 wk apart with SRS between	• Adults only • Progressive systemic disease from any histologically or cytologically confirmed solid tumor • Measurable CNS disease (≥10 mm), except for Arm C • ECOG ≤2 or KPS ≥60 • Life expectancy ≥6 wk • Stable dose of dexamethasone ≤2 mg for ≥7 d before treatment initiation	• Arm A: excludes HER2+ breast cancer, SCLC; NSCLC with targetable genomic tumor aberrations (eg, EGFR, ALK) • Known history of active TB • Immunodeficient HIV-positive participants on combination antiretroviral therapy • Prior treatment with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent	Yes

Abbreviations: ALK, anaplastic lymphoma kinase; BM, brain metastasis(es); BOIR, best overall intracranial response; CNS, central nervous system; CR, complete response; CSI, craniospinal irradiation; CTLA4, Cytotoxic T-Lymphocyte Associated Protein 4; DCR, disease control rate; DOR, duration of response; EC, extracranial; ECD, extracranial disease; ECOG, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; EIAED, enzyme-inducing antiepileptic drugs; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; HIV, human immunodeficiency virus; HR, hormone receptor; IC, intracranial; ICBR, intracranial clinical benefit rate; IF, immunofluorescence; IHC, immunohistochemistry; IT, intrathecal; IV, intravenous; IVent, intraventricular; KPS, Karnofsky Performance Status; LMD, leptomeningeal metastasis/disease, MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; NYHA, New York Heart Association; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD/PD-L, Programmed Death/Programmed Death-Ligand; PFS, progression-free survival; PK, pharmacokinetics; QoL, quality of life; RR, response rate; RT, radiotherapy; SCLC, small cell lung cancer; SRS, stereotactic radiosurgery; TB, *Bacillus Tuberculosis*; TKI, tyrosine kinase inhibitor; TT(I)R, time to (intracranial) tumor response; TTP, time to progression; UOS, unless otherwise specified; VPS, ventriculoperitoneal shunt; WBRT, whole-brain radiation therapy.

LANDSCAPE trial of lapatinib and capecitabine in HER2-positive patients with brain metastases (not specifically LM) demonstrated a promising CNS response rate of 65.9%, all of which were partial responses.[91]

Nonsmall cell lung cancer

In NSCLC, first-generation TKIs like erlotinib and gefitinib do not readily cross the BBB and may be actively removed by drug efflux proteins.[92,93] However, CSF concentrations may reach therapeutic levels at high doses.[92] Although there have been no randomized trials, responses have been described to erlotinib[94-102] and gefitinib,[103,104] particularly at high doses. Several retrospective studies have reported prolonged survival in EGFR-mutant patients who had NSCLC with LM treated with first-generation EGFR TKIs.[105,106] It is believed that second-generation and third-generation EGFR TKIs have better BBB penetration. A report of patients with pretreated EGFR-mutant NSCLC and brain metastases or LM who received afatinib on a compassionate use basis indicated a 35% response rate and CSF concentrations of up to 1 nMol.[107] Additional case reports support the efficacy of afatinib in patients with LM who have progressed on first-generation TKIs.[108,109] Preliminary data for the third-generation TKI omesartinib (AZD9291) in heavily pretreated patients with EGFR-mutant NSCLC and LM suggest promising response rates (7 of 12 patients had radiographic improvement, 8 of 9 patients had decreased EGFR messenger DNA copy numbers).[110] It is noteworthy that EGFR mutation status in the primary tumor and metastasis may be discordant, and an analysis should be performed on CSF if possible.[92,111,112] There is an ongoing phase 2 clinical trial of tesevatinib, a BBB-penetrant oral TKI, in patients with EGFR-activating mutations and brain or leptomeningeal metastases (clinicaltrials.gov identifier NCT02616393).

Anaplastic lymphoma kinase (ALK) rearrangements are another important therapeutic target in NSCLC and are associated with an increased risk of CNS involvement.[113,114] The presence of an ALK rearrangement confers sensitivity to ALK TKIs. Data suggest that second-generation inhibitors have improved BBB penetration compared with the first-generation inhibitor crizotinib. Several case reports have documented responses in LM with alectinib and ceritinib in patients with crizotinib-resistant disease.[114-116] The efficacy of ceritinib in treating LM in patients with ALK-rearranged NSCLC is being further evaluated in an ongoing phase 2 clinical trial (clinicaltrials.gov identifier NCT02336451).

Supportive Care

Symptomatic management should always be pursued in addition to any disease-directed therapies. Because symptoms may be caused by inflammation as well as direct tumor involvement, steroids may play a role in symptom management, although the role of steroids is often greater in the setting of LM secondary to hematologic malignancies. Nausea, vomiting, and headache should be treated with appropriate medications; if present, seizures should be controlled with antiepileptic drugs. Fatigue related to treatment, particularly radiation, may be alleviated by psychostimulants. If there are clinical signs of increased ICP, such as nausea, headache, or encephalopathy, then a high-volume lumbar puncture should be pursued. If pressure is elevated, then a palliative VPS should be considered.[117] Pain due to cranial and spinal nerve involvement can be managed with palliative focal radiation, opioids, or opioid-sparing agents but, unfortunately, is often refractory in the setting of a poor response to treatment of the underlying disease.

Novel Approaches

Given the remarkable response to checkpoint inhibitors in many systemic malignancies, multiple clinical trials (Table 4) are underway to evaluate their efficacy in the setting of LM, including pembrolizumab (clinicaltrials.gov identifierNCT02886585) and combination ipilimumab and nivolumab for melanoma LM (clinicaltrials.gov identifier NCT02939300). Immune-based approaches are often associated with inflammation, which, even if transient, may contribute to significant neurotoxicity in the CNS. For example, despite responses observed with IT interleukin-2 and interferon α, both were associated with significant CNS toxicity (particularly signs of meningitis, edema, and increased ICP), limiting their widespread use.[118,119] To date, there has been only 1 case report of the anticytotoxic T-lymphocyte-associated protein 4 antibody ipilimumab combined with whole-brain radiotherapy demonstrating efficacy in a patient with melanoma LM.[120]

Intrathecally delivered monoclonal antibodies against tumor-specific antigens have also been studied as a means to selectively deliver radiation (also known as radioimmunotherapy) and/or therapeutic agents. Although the approach was first studied the 1980s, it has regained interest with the renewed focus on targeted and immune-based therapies. Retrospective data and prior phase 1 trials suggest therapeutic safety and efficacy in LM across several tumor types, with particular activity observed in LM from primitive neuroectodermal tumors.[121,122] More recently, a

phase 1 study of intraventricular iodine-131-labeled monoclonal antibody 3F8 targeting ganglioside G2-positive leptomeningeal disease (primarily neuroblastoma and primary CNS tumors) demonstrated that the antibody reached therapeutic doses in the CSF, and 3 of 13 assessed patients achieved objective and/or cytologic responses.[123] A phase 2 trial of this agent is ongoing (clinicaltrials.gov identifier NCT00445965). This approach, as with other IT therapies, is limited by toxicities, such as myelosuppression, aseptic meningitis, and increased ICP. Similar to other targeted therapies, this approach is also limited by the availability of tumor-specific antibodies. There is an ongoing phase 1 clinical trial of 131-I-labeled 8H9, an antibody that targets the glycoprotein 4Ig-B7H3, which is present on a broad spectrum of solid tumors, in patients with refractory brain or leptomeningeal disease (clinicaltrials.gov identifier NCT00089245).

Novel clinical trial designs are allowing for the recruitment of patients across malignancy subtypes, often based on molecular characteristics shared across many cancers. For example, the phase 2 clinical trial for the cyclin-dependent kinase inhibitor abemaciclib includes patients with LM from breast cancer, NSCLC, or melanoma, with a particular focus on hormone receptor-positive patients (clinicaltrials.gov identifier NCT02308020). This approach may be particularly beneficial in an uncommon disease like LM, which has historically been excluded from clinical trials and is infrequent enough that accrual to dedicated trials in a single tumor subtype is prohibitively slow.

CONCLUSION

LM continues to remain one of the most challenging complications of cancer in terms of diagnostic complexity, poor prognosis, often devastating impact on quality of life, and mixed response to standard cytotoxic and targeted therapies. Treatment to date has been limited by effective drug delivery as well as toxicity; consequently, it is clear that not all patients benefit from currently available therapies. Improved diagnostic tools and better biomarkers may allow for earlier diagnosis and treatment, thereby improving outcomes. After diagnosis, optimum treatment continues to be based mostly on expert consensus because of a paucity of clinical trials. An improved understanding of the biologic mechanisms underlying tumor metastasis and the molecular features of metastatic disease compared with the primary site will allow for the testing of more targeted treatment strategies in subsets of patients most likely to benefit. Improved patient-derived xenograft models of brain metastases and LM will also assist in the discovery of new therapeutic agents and mechanisms of resistance to therapy. Evaluation of the efficacy of new treatments will be facilitated by novel trial designs and molecular-based patient selection, which have led to increased recruitment of patients with LM into clinical trials. The newly proposed RANO criteria for assessing leptomeningeal disease will help standardize response evaluation across clinical trials, although the criteria will need to be prospectively validated, and quality-of-life measures should be considered moving forward.

FUNDING SUPPORT

This work was supported by the Damon Runyon Cancer Research Foundation, the Foundation for the National Institutes of Health (grant K12CA090354), and Susan G. Komen.

CONFLICT OF INTEREST DISCLOSURES

Priscilla K. Brastianos reports personal fees from Angiochem and Genentech-Roche and grants and personal fees from Merck outside the submitted work. Nancy Wang and Mia S. Bertalan made no disclosures.

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