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Leptomeningeal metastasis: a Response Assessment in Neuro-Oncology critical review of endpoints and response criteria of published randomized clinical trials

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Purpose. To date, response criteria and optimal methods for assessment of outcome have not been standardized in patients with leptomeningeal metastasis (LM).

Methods. A Response Assessment in Neuro-Oncology working group of experts in LM critically reviewed published literature regarding randomized clinical trials (RCTs) and trial design in patients with LM.

Results. A literature review determined that 6 RCTs regarding the treatment of LM have been published, all of which assessed the response to intra-CSF based chemotherapy. Amongst these RCTs, only a single trial attempted to determine whether intra-CSF chemotherapy was of benefit compared with systemic therapy. Otherwise, this pragmatic question has not been formally addressed in patients with solid cancers and LM. The methodology of the 6 RCTs varied widely with respect to pretreatment evaluation, type of treatment, and response to treatment. Additionally there was little uniformity in reporting of treatment-related toxicity. One RCT suggests no advantage of combined versus single-agent intra-CSF chemotherapy in patients with LM. No specific intra-CSF regimen has shown superior efficacy in the treatment of LM, with the exception of liposomal cytarabine in patients with lymphomatous meningitis. Problematic with all RCTs is the lack of standardization with respect to response criteria. There was considerable variation in definitions of response by clinical examination, neuroimaging, and CSF analysis.

Conclusion. Based upon a review of published RCTs in LM, there exists a significant unmet need for guidelines for evaluating patients with LM in clinical practice as well as for response assessment in clinical trials.

The term "leptomeningeal metastasis" (LM), also known as neoplastic meningitis, refers to involvement of the cerebrospinal fluid (CSF) and leptomeninges (pia and arachnoid) by any solid tumor or hematologic malignancy. When caused by systemic cancer, LM is often called carcinomatous meningitis or meningeal carcinomatosis and is reported in 4%–15% of patients with cancer.[1–13] Lymphomatous or leukemic meningitis occurs in 5%–15% of patients with lymphoma or leukemia.[1–13] LM is the third most common metastatic complication affecting the central nervous system (CNS) after brain metastases and epidural spinal cord compression, with 7000–9000 new cases diagnosed annually in the United States.[1–13] In decreasing order, the most

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common sources of systemic cancer metastatic to the leptomeninges are breast, lung, melanoma, aggressive non-Hodgkin' lymphoma, and acute lymphocytic leukemia.

Leptomeningeal metastasis usually (>70%) presents in the setting of active systemic disease but can present after a disease-free interval (20%) and even be the first manifestation of cancer (5%).[1–13] A diagnosis of LM must be considered in patients with cancer and neurologic symptoms.[1–13] Neurologic dysfunction most commonly involves one or more segments of the neuraxis, including cerebral hemispheres, cranial nerves, spinal cord, or spinal roots. Because any site in the CNS may be involved, clinical manifestations of LM overlap significantly with those of parenchymal brain metastases, treatment-related toxicities, metabolic disturbances, and, rarely, neurologic paraneoplastic syndromes.

Clinical manifestations that strongly suggest the diagnosis of LM include cauda equina symptoms or signs, communicating hydrocephalus, and cranial neuropathies. Early in the disease, neurologic involvement can be subtle, such as an isolated diplopia or radicular pain.[1–13] In some patients, cerebral hemisphere symptoms such as altered mental status or seizures may predominate. Neuroimaging (ie, MRI of brain or spine) may suggest LM based upon focal or diffuse enhancement of the leptomeninges, nerve roots, or ependymal surface and, in the context of a patient with cancer and low likelihood of infectious meningitis, may be diagnostic of LM. Brain parenchymal metastases from nonhematologic cancers coexist in 38%–83% of LM patients.[14–18] The reported rates of negative CNS imaging in patients with LM range from 30% to 70%, thus normal CNS imaging does not exclude a diagnosis of LM. CSF analysis is crucial to diagnosing LM, as in nearly all patients some abnormality of CSF opening pressure, protein, glucose, or cell count will be apparent.[5,9,19] The finding of tumor cells in CSF establishes a definitive diagnosis of LM (excluding patients within 2 wk of a CNS tumor resection), but a single CSF analysis has a high false negative rate (nearly 50%) for positive cytology even when multiple large volume (>10 mL) samples are sent for cytologic examination and prompt processing methods are utilized.[5] Repeated CSF analysis when initially negative increases the chances of finding malignant cells to 80% or more. CSF tumor marker concentrations are of unproven value, with the exception of nonseminomatous germ cell tumors.[20,21] In patients with hematologic cancers, CSF flow cytometry is more sensitive than CSF cytology and additionally requires a comparatively smaller volume of CSF (<2 mL) for analysis. The most specific ancillary study results (ie, positive cytology, abnormal flow cytometry [in hematologic cancers], and abnormal neuroimaging) can be negative or inconclusive in LM. The diagnosis of probable LM is made in patients with cancer when neurologic symptoms are suggestive for LM, associated with nonspecific CSF abnormalities and negative or inconclusive MRI studies.

Two particular challenges arise in the treatment of LM: (i) deciding whether to treat and (ii) if LM-directed treatment is considered, deciding *how* to treat (radiotherapy, surgical intervention, systemic or intra-CSF chemotherapy).[1–13,22–27] The optimal patients for treatment include those with low tumor burden as reflected by functional independence and lack of major neurologic deficits, no evidence of bulky CNS disease by neuroimaging, absence of CSF flow block by radioisotope imaging, expected survival >3 months, and limited extraneural metastatic disease.[28,29] CNS imaging studies commonly recommended prior to treatment are neuraxis MRI and, in patients considered for treatment with intra-CSF chemotherapy, a radioisotope CSF flow study; the latter is recommended in guidelines but infrequently utilized.[30,31] Flow studies assist in determining whether intra-CSF chemotherapy will distribute homogeneously throughout the CSF. If CSF is compartmentalized or flow impaired, therapeutic concentrations of chemotherapy may not reach all sites of disease and may be associated with increased risk of treatment-related neurotoxicity.[30,31] If intra-CSF chemotherapy treatment is believed warranted, a decision is made whether to treat by lumbar administration (intrathecal) or via a surgically implanted subgaleal reservoir and intraventricular catheter (ie, an Ommaya, Sophysa, or Rickham reservoir system).[32]

The role of surgical intervention in LM is largely limited to placement of a ventriculoperitoneal shunt in patients with symptomatic hydrocephalus, implantation of an intraventricular catheter and subgaleal reservoir for administration of cytotoxic drugs, or, very occasionally, obtaining a meningeal biopsy for pathological confirmation of LM.[1–13,22] Radiotherapy is used in the treatment of LM[1–14] to palliate symptoms, such as cauda equine syndrome and cranial neuropathies, to decrease coexistent bulky disease and correct regional areas of impaired CSF flow when patients are treated with intra-CSF chemotherapy. Common regimens are 20–30 Gy in 5–10 fractions to whole brain or to a partial spine field. Whole-neuraxis irradiation is often avoided in the treatment of LM from solid tumors, because it is associated with significant bone marrow toxicity and has not been shown to offer a therapeutic advantage.

High-dose systemic chemotherapy with methotrexate (MTX) and cytarabine may result in cytotoxic CSF concentrations, theoretically obviating the need for intra-CSF chemotherapy.[25–27] However, the majority of systemic chemotherapy and many targeted chemotherapies, such as imatinib, lapatinib, rituximab, and trastuzumab, do not penetrate the intact blood–brain barrier in adequate concentrations—thus, the CNS including CSF may become a "sanctuary site" with such treatments. However, systemic chemotherapy has a role in the treatment of LM as an adjunct treatment of extraneural disease and possibly bulky subarachnoid disease.[1–13,25–27] Importantly, intra-CSF chemotherapy commonly used in the treatment of LM is based upon limited studies with small numbers of patients and it has never been clearly established as an effective treatment for LM in a prospective randomized trial.[32–38]

Randomized Clinical Trials in Leptomeningeal Metastasis: An Overview of Results

Six randomized clinical trials (RCTs) have been conducted in LM: 5 have been published in full and 1 in abstract form only[32–38] (Table 1). Leptomeningeal metastasis from various primary cancers was evaluated in all but 1 study. In 5 of the RCTs, different intra-CSF chemotherapies were compared, while in 1 (breast cancer–related LM only), systemic therapy and involved-field radiotherapy with or without intra-CSF MTX were compared.[37] Amongst the various RCTs, the numbers of patients were small and varied from 28 to 103. Additionally the studies accrued slowly, as assessed by the time for recruitment (2–7 y). One trial was closed prematurely because of poor accrual. All studies were multicenter and open-label.

Table 1. Randomized clinical studies in leptomeningeal metastasis

Study	Design	Response	Toxicity
Hitchins 1987[32]	$n = 44$ 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% Intracranial hemorrhage: 11%
Grossman 1993[34]	$n = 59$ Solid tumors and lymphoma (in 90%) IT MTX vs thiotepa	IT MTX vs IT thiotepa: Neurologic improvements: none Median survival: 15.9 vs 14.1 wk	IT MTX vs thiotepa: Serious toxicity (47%) similar between groups Mucositis and neurologic complications more common in IT MTX group
Glantz 1999[35]	$n = 28$ Lymphoma DepoCyt vs Ara-C	IVent DepoCyt vs IVent Ara-C: RR*: 71% vs 15% TTP*: 778.5 vs 42 d OS*: 99.5 vs 63 d	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 1999[36]	$n = 28$ 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% Bacterial meningitis: 10% vs 3%
Boogerd 2004[37]	$n = 35$ Breast cancer Systemic therapy and involved-field radiotherapy with IT vs no IT MTX	Systemic therapy and involved-field radiotherapy with IT MTX vs no IT MTX: Improved stabilization: 59% vs 67% TTP*: 23 vs 24 wk OS: 18.3 vs 30.3 wk	Systemic therapy and involved-field radiotherapy with IT MTX vs no IT MTX: Treatment complications: 47% vs 6%
Shapiro 2006[38]	Solid tumors: $n = 103$ DepoCyt vs MTX Lymphoma: $n = 24$ DepoCyt vs Ara-C	IVent DepoCyt vs IVent MTX/Ara-C: PFS*: 35 vs 43 d IVent DepoCyt vs IVent MTX: PFS*: 35 vs 37.5 d IVent DepoCyt vs IVent Ara-C: CytR*: 33.3% vs 16.7%	IVent DepoCyt vs IVent MTX/Ara-C: Drug-related AEs: 48% vs 60% Serious AEs: 86% vs 77%

Abbreviations: AE, adverse event; Ara-C, cytarabine; CytR, cytologic response; N/V, nausea/vomiting; OS, overall survival; RR, response rate; TTP, time to progression; IVent, intraventricular chemotherapy; IT, intralumbar chemotherapy.
*No significant differences between groups;

Hitchins et al[32] reported on 44 patients with LM from solid tumors ($n = 41$) or lymphoma ($n = 3$). Patients were randomized to intra-CSF MTX or intra-CSF MTX plus cytarabine.[32,33] Twenty-six patients were treated by intra-CSF MTX by lumbar puncture and 18 by a ventricular access device. Response rates (61% vs 45%) and median overall survival (12 vs 7 wk) were not significantly different between treatment arms. Six patients (18%) developed purulent meningitis (4 with a ventricular device). In addition, 5 patients (28%) with a ventricular device had major device-related complications. Cause of death was LM in 35% (15 patients), concurrent systemic disease in 56%, and complications of treatment in 9%.

Grossman et al[34] compared intra-CSF MTX to intra-CSF thiotepa in 59 patients with LM, 52 of whom were assessable (solid tumors in 42, lymphoma in 10). No complete responses were observed, but 12 patients (23%) had stable disease at the 8-week evaluation. Median survival was similar in both treatment arms (15.9 vs 12.1 wk). Median survival was longer (17 wk) in the 18 patients with conversion of CSF cytology. Serious toxicity was similar in both groups, but mucositis and neurologic complications such as headache were more frequent in patients who received MTX. Treatment-related toxicity was fatal in 2 patients (4%), life threatening in 8 (15%), and severe in 14 (27%), but not significantly different between treatment arms.

Glantz et al[35] studied 28 patients with lymphomatous meningitis and compared intra-CSF liposomal cytarabine to standard intra-CSF cytarabine. The response rate significantly favored liposomal cytarabine (71% vs 15%, $P = .006$). Time to neurologic disease progression (78 vs 42 d) and median survival (99 vs 63 d) were not significantly different. Treatment-related toxicity was similar in both treatment arms (grade ≥3 in 12%) and manifested exclusively as transient chemical meningitis.

In a companion study, Glantz and colleagues[36] reported on 61 patients with solid tumor–related LM comparing intra-CSF liposomal cytarabine to intra-CSF MTX. Rates of response (26% vs 20%), median survival (105 vs 78 d), treatment-related grade ≥3 toxicity (5% vs 3%), and cause of death due to LM (46% vs 62%) were similar. Time to neurologic progression, however, was longer in the liposomal cytarabine arm (58 vs 30 d, $P = .007$).

Boogerd et al.[37] compared systemic therapy and involved-field radiotherapy with or without intra-CSF MTX in 35 breast cancer patients with LM. No difference in clinical response (neurologic improvement: 41% vs 39%; disease stabilization: 18% vs 28%) or median survival (18.3 vs 30.3 wk) in the intra-CSF versus no intra-CSF chemotherapy group was seen.[27] Treatment-related complications were seen in 47% of patients in the intra-CSF chemotherapy arm compared with 6% in the no intra-CSF chemotherapy arm.

Shapiro et al[38] reported, in abstract form only, on 103 patients with solid tumor–related LM comparing intra-CSF liposomal cytarabine to intra-CSF MTX. In addition, 25 patients with lymphomatous meningitis were treated, comparing intra-CSF liposomal cytarabine with standard intra-CSF cytarabine. Progression-free survival (PFS) in the total cohort did not differ between treatment arms (35 d with liposomal cytarabine vs 43 d in the other treatment arm). Additionally, PFS did not differ in the solid tumor group; but in the lymphoma group, cytologic response (33% in the liposomal cytarabine vs 17% in the other treatment arm) and PFS (34 vs 50 d) were improved with intra-CSF liposomal cytarabine.[26] Drug-related adverse events were similar (48% vs 60%) in both arms.

The above-mentioned RCTs suggest that intra-CSF chemotherapy may have modest benefit in the treatment of LM, but outcome with treatment remains very unsatisfactory (median overall survival 3 mo) and is often associated with treatment-related toxicity. Furthermore, it is unclear whether there is a significant advantage of any specific intra-CSF chemotherapy agent used in carcinomatous meningitis. The one study that addressed multi-agent intra-CSF chemotherapy relative to single agent therapy found no advantage. Lastly, the role of intra-CSF chemotherapy in the treatment of carcinomatous meningitis has never been definitively established and, based upon the study by Boogerd et al[37] may have minimal impact on survival compared with systemic therapy and CNS-directed radiotherapy.

Randomized Studies in Leptomeningeal Metastasis: Shortcomings in the Choice of Endpoints and Response Criteria

Four intra-CSF chemotherapy agents were used in the above-mentioned RCTs: MTX, cytarabine (cytosine arabinoside; Ara-C), liposomal cytarabine (DepoCyt), and thiotepa, either as single agents or in combination[24,32–38] (Table 2). Primary endpoints were heterogeneous across trials and consisted of overall survival, neurologic response rate, time to neurologic progression, and PFS. Secondary endpoints also varied across the RCTs and included time to neurologic progression, neurologic response rate, cause of death, safety and toxicity profile, survival, KPS evolution over time, LM-specific survival, and quality of life. Response criteria were based on the combination of clinical, radiologic (MRI exclusively), and cytologic data but differed from one study to another. In the trial limited to breast cancer, the evaluation of response was based on clinical assessment only.[37] Response consisted of significant neurologic improvement of at least one symptom or sign without deterioration of other neurologic symptoms/signs. Progression was defined as a deterioration of symptoms/signs or appearance of new neurologic symptoms/signs of LM. Significant improvement was not defined, and its assessment appeared to be subjective and not quantifiable. Moreover, changes in neurologic symptoms and signs may be secondary to LM, parenchymal brain metastases, neurotoxicity of treatment, or intercurrent disease. Distinction among these causes may be difficult, as they may co-occur. Responses based on cytology differed according to the RCT. In the studies of liposomal cytarabine, complete responders were defined as patients in whom a negative CSF cytology was achieved from all sites that were known to be positive at study entry; in addition, stability of neurologic symptoms and signs was required.[35,36] In other studies, a complete response required normalization of CSF (cytology, chemistry, and cell count) replicated at a second timepoint 4 weeks later.[32–34] Importantly, the CSF definitions of partial response, improvement, stable disease, and progression are variable from one study to another and are problematic, as these definitions introduce the concept of quantitative CSF cytology (eg, a 50% decrease or a 25% increase in CSF tumor cell count), an assessment that is not routinely performed in cytology laboratories and lacks validation. Uniformly, all RCTs required clinical and CSF cytology assessments before each cycle of treatment. Importantly, details of radiologic assessments (frequency, site of neuraxis evaluated, definitions of response) were not reported. No MRI criteria were defined. Cranial CT and myelograms were assessed in 2 studies.[32–34] One study mentioned bidirectional measurements of the subarachnoid nodules.[32] An assessment of treatment-related toxicity was stated in 4 studies only[34,36–38] (Table 3). Most often, grading of adverse events was based on the Common Toxicity Criteria (standard criteria of the Eastern Cooperative Oncology Group, expanded by the Cancer and Leukemia Group B). Particular attention was directed to treatment-related leukoencephalopathy and arachnoiditis (chemical meningitis).

In summary, the RCTs for LM did not utilize standard assessment methodology, and consequently response definitions vary widely across trials. CSF cytology and clinical evaluation are universally agreed upon as relevant response criteria, but the role of CNS imaging (either pretreatment or while on study) has never been established in an RCT. Importantly, assessment of CSF varied, as some trials required normalization of all CSF parameters (chemistry, cell count, and cytology) for a definition of response to treatment. Additionally the RCTs were inconsistent in reporting toxicity, an aspect of treatment that is both common and challenging in managing this disease. The RCTs therefore indicate an unmet need in LM for harmonization with respect to method of evaluation and response criteria when treating patients both on and off clinical trials.

Table 2. Methods of assessment in RCTs in leptomeningeal metastasis

Study	Endpoints of the Study	Criteria of Evaluation	Clinical Evaluation	MRI Evaluation	Cytologic Evaluation
Hitchins 1987[32] Patients with documented LM from various cancers IT MTX vs IT MTX + Ara-C	*Primary endpoint:* Response rate *Secondary endpoint:* Median survival Toxicity	*Complete response:* Improved clinical status, negative CSF cytology, and normalization of CSF biochemistry, all persisting ≥4 wk. *Partial response:* Improvement or stable clinical status, negative CSF cytology, and substantial (>50%) improvement in CSF biochemistry persisting ≥4 wk. *Stable disease:* Stable clinical status, negative CSF cytology, and substantial (>50%) improvement in CSF biochemistry persisting ≥4 wk. *Progressive disease:* Failed to meet the criteria for response	All neurologic symptoms and signs documented at the inclusion and before each course of treatment	CT scan and myelogram repeated every 8 wk, if abnormal at entry	CSF samples at baseline and before each course Cytology, biochemistry (protein and glucose), and microbiology
Grossman 1993[34] Patients with LM treated with IT MTX vs thiotepa histologically confirmed LM	*Primary endpoints:* Neurologic response rate Survival *Secondary endpoints:* Prognostic factors for response and survival Toxicity	*Complete response:* A completely normal neurologic examination, negative lumbar and ventricular CSF cytology, no meningeal masses by radiologic studies, and normal CSF protein and glucose levels *Improvement:* Patients neurologically better with a 50% decrease in CSF tumor cells or a 50% shrinkage in the bidirectional measurement of subarachnoid masses *Stable disease:* <50% improvement in the number of tumor cells or meningeal masses without evidence of progression *Progression disease:* Failed to meet the criteria for response	All neurologic symptoms and signs documented at the inclusion and before each course of treatment	CT scan and myelogram repeated every 8 wk, if abnormal at entry	CSF samples at baseline and before each course; cytology, biochemistry (protein and glucose), and microbiology
Glantz 1999[35] Patients with lymphoma and positive CSF cytology were randomized to receive IT/IVent liposomal Ara-C vs nonliposomal Ara-C	*Primary endpoint:* Neurologic response rate *Secondary endpoints:* Time to neurologic progression: time from first day of study treatment and day of neurologic progression Survival from time of study entry Comparison in KPS between baseline and the end of induction phase Safety	*Response:* If the CSF cytology converted from positive to negative at all sites previously shown to be positive and patients remained neurologically stable at the time of the CSF examination *No response:* Positive or suspicious cytology at the end of the induction period (day 29) or if patients suffered neurologic progression despite having negative cytology	Before each cycle of therapy, patients underwent a complete neurologic assessment, measurement of hematologic and serum chemistry parameters, and a urinalysis	Not stated	An independent cytopathologist, blinded to the drug assignment and chronology of CSF samples, reviewed all available CSF cytology slides after the patient completed the study CSF cytology results were reported as either unsatisfactory, negative, abnormal (scored as negative), suspicious (scored as positive), or malignant Treatment decisions were based on the interpretation of the local cytopathologist. Efficacy analysis based on the interpretation of a central cytologist

Glantz 1999[36] RCT of IT liposomal Ara-C vs MTX in patients with solid tumor neoplastic meningitis histologically proven LM	*Primary endpoints:* Response rate at the end of the induction period Time to neurologic progression: time from the start of treatment until neurologic progression or death, whichever comes first *Secondary endpoints:* Overall survival Neoplastic meningitis–specific survival: time from the start of treatment until death due to the meningeal component. Patients dying from other causes (including progression of their systematic disease) were censored in this analysis Safety *Quality of life*: FACT CNS scale	*Response:* Negative CSF cytology from all sites that were known to be positive at the study entry, plus a stable or improved neurologic examination Patients who met the criteria for cytologic conversion, irrespective of whether they had progressed neurologically, were termed "cytologic responders." *No response*: A single positive CSF cytology at the end of induction, 2 consecutive suspicious CSF cytologies, or evidence of LM progression on neurologic examination	General and standardized neurologic examinations every 14 d during the induction period and first month of the consolidation and then monthly until CSF relapse or death	Not stated	Independent central review of all CSF cytology by one cytopathologist who was blinded to drug assignment and the chronology of CSF samples
Boogerd 2004[37] Patients with LM from breast cancer were randomized to IT/IVent chemotherapy vs no IT/IVent treatment. Both groups received systemic chemotherapy and involved-field radiotherapy when clinically appropriate diagnosis of LM on clinical characteristics of LM, confirmed by tumor-positive CSF cytology, on CSF biochemical abnormalities combined with characteristic findings on MRI	*Primary endpoint:* Overall survival: time from randomization until death *Secondary endpoints:* Time to neurologic progression: time from neurologic stabilization or response until neurologic progression Neurologic response rate Cause of death Toxicity of treatment	*Response:* Significant neurologic improvement of at least one symptom or sign without deterioration of other neurologic symptoms/signs *Stable disease:* No significant change in existing neurologic symptoms/signs *Progression:* Deterioration of symptoms/signs or appearance of new neurologic symptoms/signs of LM	General and neurologic examinations at diagnosis and every 2 wk during the first 2 mo and monthly thereafter until neurologic progression	Neuroimaging was not used to evaluate neurologic response	Not stated
Shapiro 2006[38] Comparison of patients' benefit and safety of IT cytarabine liposome injection with MTX or nonliposomal Ara-C against solid tumor and lymphomatous neoplastic meningitis *Solid tumor patients:* Liposomal Ara-C vs MTX Lymphoma patients: Liposomal Ara-C vs nonliposomal Ara-C *Patients had either histologically documented LM or symptomatic meningeal tumor verified by MRI or CT	*Primary endpoint:* PFS: randomized to neurologic progression or death *Secondary endpoint:* Not stated Safety	Not stated	Not stated	Not stated	Not stated

Ara-C, cytarabine; FACT, Functional Assessment of Cancer Therapy; N/V, nausea/vomiting; IVent, intraventricular chemotherapy; IT, intralumbar chemotherapy.

Table 3. Toxicity in RCTs in leptomeningeal metastasis

Study	Evaluation of Toxicity
Hitchins 1987[32]	Not stated (most frequent side effects reported)
Grossman 1993[34]	Most frequent side effects reported according to ECOG standard criteria by degree, type, and cause
Glantz 1999[35]	Identification of episodes of arachnoiditis was based on a standardized algorithm.
Lymphoma	Patients were scored as having drug-related arachnoiditis within 4 d of drug injection if they developed neck rigidity, neck pain, or meningismus or if they developed any 2 of the following signs or symptoms at the same time: nausea, vomiting, headache, fever, back pain, aseptic CSF pleocytosis. Arachnoiditis was graded on the basis of adverse events captured by the algorithm as mild (grade 1), moderate (grade 2), severe (grade 3), or life threatening (grade 4).
Glantz 1999[36]	CALGB expanded Common Toxicity Criteria
Solid tumors	Complete physical and neurologic examinations, complete blood counts, serum chemistries, liver enzymes, creatinine, urinalysis, and CSF examinations for WBCs and RBCs; measures of glucose, protein, and malignant cells were performed before each cycle of therapy, monthly after the conclusion of treatment, and at additional points when clinically indicated. Drug-related meningitis was defined as the abrupt appearance within 4 d of intra-CSF drug administration, of neck or back pain, neck stiffness, or any 2 of the following signs or symptoms: (a) headache, (b) nausea, (c) vomiting, (d) fever, (e) lethargy, or (f) culture-negative CSF pleocytosis. Drug-related meningitis was graded as: mild (grade 1), moderate (grade 2), severe (grade 3), or life threatening (grade 4), based on the severity of the worst component symptom or sign. Quality of life was evaluated by administering the FACT-CNS scale at both study entry and the end of the induction period. The FACT-CNS scale consists of the FACT-General scale plus a scale for "additional concerns" containing 12 supplementary items designed specifically for use in the patients with neoplastic meningitis. The trial prospectively documented adequate internal consistency of this instrument and its sensitivity to the response attained by the patient.
Boogerd 2004[37]	For the assessment of neurotoxicity, all events including appearance of signs that were not clearly related to LM were recorded. Leukoencephalopathy was evaluated according to a neurotoxicity scoring list specific for signs of subcortical dementia and including cognitive functioning, vigilance, and gait disturbances. Toxicity was scored as normal, moderately impaired, or seriously impaired. To establish the diagnosis of leukoencephalopathy, MRI should show characteristic T2 hypersensitivity involving the periventricular white matter.
Shapiro 2006[38]	Not stated

Abbreviations: ECOG, Eastern Cooperative Oncology Group; CALGB, Cancer and Leukemia Group B; RBC, red blood cells; WBC, white blood cells; FACT, Functional Assessment of Cancer Therapy.

Challenges and Controversies in Leptomeningeal Metastasis

Leptomeningeal metastasis is a disorder that presents substantial challenges to clinicians in everyday practice as well as to clinical researchers. Diagnostic criteria are not standardized, treatment effectiveness is low, and there are no generally accepted criteria that define patient subgroups that might benefit from therapy. In addition, patients have often been heavily pretreated with chemotherapy for systemic disease with few remaining therapeutic options, resulting in refractory concomitant systemic disease.

Several factors contribute to the difficulty in evaluating new therapies for LM. Traditional survival endpoints, although definitive, are difficult to apply in LM, as patients often have simultaneous progression of both systemic and CNS disease. The cause of death, whether it be neurologic, systemic, combined, treatment-related neurotoxicity, or intercurrent disease, is usually difficult to determine in this population. Consequently the best endpoint of treatment may be time to neurologic disease progression. The presence of malignant cells in CSF is the definitive test for LM, but false negative testing is very common, possibly in up to 50% of all patients with carcinomatous meningitis.[5] As a result, CSF cytology is a poor surrogate marker for disease response in LM. Similarly, false negative results are common with neuroimaging, with 30% or more patients not showing meningeal enhancement or other LM-related abnormalities on MRI.[17,18] Moreover, the sensitivity of MRI for diagnosing LM is less in patients with hematopoietic malignancies compared with patients with solid tumors.[39–41] Additionally for most patients with solid tumors, reduction in leptomeningeal enhancement on MRI is not commonly observed with intra-CSF or systemic chemotherapy. Lastly and importantly, there currently exists no validated quantitative method to assess radiographic disease in LM, and imaging changes often do not correlate with the clinical status of the patient. Thus, the low response rates to existing treatments and the limitations of modalities of assessment leave considerable uncertainty as to how to best assess LM. In the future, rare cell capture technology could enter widespread use to detect circulating tumor cells in the CSF, potentially providing earlier diagnostic confirmation.[39–41] Soluble biomarkers of disease in the CSF—for example, vascular endothelial growth factor—may become useful as surrogates of disease burden, but their utility needs to be further validated.[21] The reproducibility of CSF biomarker levels can be

Table 4. Phase II trials of novel intra-CSF agents

Authors (reference)	# Patients	Tumor Histology	Agent	Dose/Schedule	Median Time to Tumor Progression (wk)	Median Overall Survival (wk)	CSF Cytology Response	MRI Response
Groves 2008[44]	62	Solid cancers	Topotecan	0.4 mg/biw	7	15	21%	10% PR 44% SD
Chamberlain 2006[45]	27	Solid cancers	Etoposide	0.5 mg/qd	8	10		26% PR/CR 44% SD
Blaney 2005[46]	33	Mixed solid & hematologic cancers	Mafosfamide	3.5–6.5 mg/qwk	NR	NR	24%	NR
Rubenstein 2007[47]	10	Lymphoma	Rituximab	10, 25, 50 mg/biw	NR	NR	60%	10%
Rubenstein 2013[48]	14	Lymphoma	Rituximab + MTX	10 and 25 mg (rituximab) + 12 mg/biw (MTX)	NR	NR	75%	43%
Chamberlain 2002[49]	22	Solid cancers	α-interferon	1×106 IU tiw	16	18	45%	NR
Chamberlain 2009[50]	14	Lymphoma	Rituximab + liposomal cytarabine	25 mg biw (rituximab) and 50 mg qow (liposomal Ara-C)	16	20	71%	NR

Abbreviations: biw, twice per week; qd, once daily; qwk, once per week; tiw, 3 times per week; qow, every other week; NR, not reported; PR, partial response; SD, stable disease; CR, complete response.

affected by CSF flow dynamics, so this will need to be incorporated into their development.

Other issues involving LM need to be addressed. There are no compelling data to suggest that steroids have a role in the treatment of LM outside of their use for associated brain metastases and intra-CSF chemotherapy-related arachnoiditis. Consequently steroid use and dose are not considered as part of LM response criteria, notwithstanding frequent use in LM. At present, the optimal role for radiation or systemic and intra-CSF therapy, or both, is unclear. The benefit of intraventricular drug administration over intralumbar treatment has not been established in a prospective manner for adult solid tumor malignancies.[32,33] It is unclear whether intra-CSF chemotherapy should be offered to LM patients who require ventriculoperitoneal shunts due to hydrocephalus, which alters CSF pharmacokinetics for drugs administered into CSF.[21]

Perhaps the greatest challenge is the lack of effective therapies beyond palliative irradiation to symptomatic or bulky sites of disease. For intra-CSF use, only 4 drugs are commonly used: MTX, cytarabine, liposomal cytarabine, or thiotepa for carcinomatous meningitis; MTX and cytarabine for leukemic meningitis; and liposomal cytarabine and MTX for lymphomatous meningitis.[24,32–38] Even though these agents have shown modest evidence of LM activity, the optimal dosing and schedule of intra-CSF administration and the role of maintenance therapy have not been standardized. Further, current intra-CSF agents have limited single agent activity in adult solid tumors. Finally, there are no systemic agents with established efficacy for LM, with the possible exceptions of high-dose systemic MTX (breast cancer and lymphoma) and perhaps high-dose cytarabine (leukemia and lymphoma).[26,27] Systemic agents targeting the primary cancer according to tumor histology, such as fluoropyridines in breast cancer, may have some efficacy, as impairment of the blood–meningeal barrier has been observed in LM, but the role of systemic chemotherapy as a primary LM-directed therapy remains to be defined and validated.[42] Currently and based upon available literature, the respective roles of intra-CSF versus systemic therapy have yet to be defined in RCTs of LM. There are several small phase II trials suggesting efficacy for a number of agents administered intra-CSF (etoposide, topotecan, interferon-alpha, rituximab, and trastuzumab), but none has been prospectively evaluated in an RCT[43–51] (Table 4).

Conclusions

There is an unmet need in LM with respect to both the initial diagnostic assessment and the parameters for determining response to treatment regardless of patient participation in clinical trials. The above-mentioned RCTs all share several common initial assessment tools, including determination of CSF cytology, and positive CSF cytology has been a universal inclusion criteria for entry into all published RCTs. All RCTs have required a neurologic examination documenting any deficits, and a robust performance status has been required in all. Nonetheless, currently in neuro-oncology there is no standardized method to assess the neurologic examination, and consequently RCTs in LM lack a rigorous method to determine disease progression. Also poorly defined are the utility of pretreatment neuroimaging with respect to inclusion into a clinical trial, how radiographic findings should affect treatment, and how to use neuroimaging as a response

instrument independent of CSF cytology or neurologic examination. Further RCTs are needed to determine the role of both intra-CSF and systemic chemotherapy in LM and hopefully define specific therapies for specific cancers metastasizing to the CSF and leptomeninges. This is the first comprehensive review of LM performed by an international panel of experts from the United States and Europe (the RANO Group) that has critically reevaluated the endpoints and response criteria across published randomized studies. Based on this preliminary work, the group is constructing a second paper aimed at proposing new response criteria to be validated in future clinical trials in LM. It is hoped that through this effort, standardized approaches for LM evaluation, criteria for response to treatment, and defined endpoints for clinical trials will be available and ultimately validated.

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