Review Article on Palliative Care in Neuro-Oncology

An overview of leptomeningeal disease

Timothy K. Nguyen[1], Eric K. Nguyen[2], Hany Soliman[3]

[1]Department of Radiation Oncology, London Health Sciences Centre, Western University, London, ON, Canada; [2]Department of Radiation Oncology, Juravinski Cancer Center, McMaster University, Hamilton, ON, Canada; [3]Department of Radiation Oncology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada

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Correspondence to: Dr. Timothy Nguyen. Assistant Professor, Department of Radiation Oncology, London Health Sciences Centre, Schulich School of Medicine & Dentistry, Western University, London, ON, Canada. Email: Timothy.Nguyen@lhsc.on.ca.

Abstract: Leptomeningeal disease (LMD) is a poor prognosis pattern of disease progression in patients with metastatic malignancy with limited treatment options. Patients may be asymptomatic or present with non-specific neurologic deficits, therefore gadolinium-enhanced magnetic resonance imaging of the brain and spine is critical for establishing a diagnosis. Although the treatment intent is palliative in the context of LMD, a multidisciplinary approach is still important to ensure patients receive a timely diagnosis and appropriate treatment to maximize symptom control and preserve quality of life. Radiotherapy is typically delivered to the whole brain or focal spinal regions for the purposes of treating bulky disease, stabilizing symptoms, or relieving cerebrospinal fluid obstruction. Whole craniospinal irradiation (CSI) is generally avoided given its toxicity profile and should only be considered in carefully selected patients where the potential benefit may outweigh the adverse effects. CSI with proton radiotherapy (oppose to conventional photon radiotherapy) has shown promise with improved toxicity for patients with primary CNS tumors. This may be a preferred option for patients being considered for CSI at centres with the proton therapy capabilities. Focal hypofractionated stereotactic radiotherapy (SRT) to intracranial targets is an emerging approach to LMD that may be useful in select patients with limited disease particularly in the setting of reirradiation. Chemotherapies may be delivered intrathecally, although the evidence supporting its efficacy is limited and heterogeneous in regards to the tumor sites examined. Finally, targeted therapy and novel applications of immune checkpoint inhibitors are promising; however, further research is required to guide the use of these agents.

Keywords: Leptomeningeal; metastases; radiotherapy; chemotherapy

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Epidemiology

Leptomeningeal disease (LMD) is the infiltration of tumor cells into the leptomeninges, subarachnoid space and other cerebral spinal fluid (CSF) compartments. It occurs in approximately 5–8% of patients with solid tumors and 5–15% of patients with hematologic malignancies (1). LMD is considered a disease of the "sanctuary" space, where the blood-brain barrier restricts both tumor cells and therapeutic medications (2). While advances in systemic therapies have improved overall disease control, their penetrance into the central nervous system (CNS) is poor given the blood brain barrier, resulting in longer survival in patients with a hyphenate propensity CNS metastases including LMD (3,4). LMD presents as the initial manifestation of metastatic cancer in 5–10% of patients, but more commonly develops in the setting of progressive disease with the median time from the diagnosis

of metastatic disease to LMD ranging from 1.2–2 years in solid tumors (5). Synchronous intraparenchymal brain metastases are found in approximately 11–31% of cases (6).

Pathogenesis

Metastatic spread into the leptomeninges and CSF compartments can occur through one of several avenues. Tumor cells can reach these areas through the vasculature of the arachnoid or choroid plexus, by growing along nerve and vascular sheaths, through dissemination in lymphatic channels, or by direct extension via parenchymal brain metastases or bony lesions adjacent to the meninges (2,7). Previously, the mechanisms by which tumor cells penetrate the blood-brain and blood-CSF barrier were poorly understood; however, recent evidence suggests that cancer cells invading the CSF have upregulated production of complement component 3 (C3), which can affect the permeability of the epithelial barriers similar to what has been previously described in renal and pulmonary tissues (8). Increased C3 leads to activation of C3a receptors in the choroid plexus epithelium, disrupting the blood-CSF barrier and allowing entry of plasma growth factors which ultimately stimulate cancer cell proliferation (9). Compared to patients with only parenchymal metastases, C3 levels in the CSF were found to be higher suggesting that complement levels may be predictive for LMD and presents a potential target for novel treatments. Whether C3 acts as a main driver to induce epithelial permeability, or is simply a by-product of primary inflammation that stimulates BBB invasion is yet to be determined.

Clinical presentation

LMD typically presents with non-specific neurological signs and symptoms that tend to progress insidiously over time. On imaging, patients may present with focal sites of enhancing disease or a more diffuse pattern with the entire neuraxis at potential risk. As result, the presenting symptoms may be findings are usually attributable to dysfunction of the cranial nerves, cerebellum, spine, or increased intracranial pressure (2,7). Examples of common symptoms include headache, altered mentation, nausea, and vomiting, as well as symptoms related to radiculopathies, myelopathies, and cauda equina syndrome (6,10). Oculomotor, facial, and cochlear nerves are often affected causing diplopia, facial weakness, and changes in hearing (1). Given the nonspecific symptomatology, it is important to exclude alternative diagnoses such as infectious meningitis, treatment-related effects, and paraneoplastic syndromes (11). General suggestions for symptom management in patients with LMD are provided in *Table 1*.

Risk assessment

The National Comprehensive Cancer Network (NCCN) stratifies patients with LMD into "good risk" and "poor risk" categories based on clinical features (21). Good risk patients have a Karnofsky Performance Status (KPS) of ≥60, no major neurologic deficits, minimal systemic disease and reasonable systemic treatment options. Poor risk patients have a KPS of <60, major neurologic deficits, extensive systemic disease, few treatment options, bulky CNS disease, and/or encephalopathy. Best supportive care with or without palliative radiotherapy should be considered for poor risk patients rather than aggressive systemic therapy given their condition and limited survival. Similarly, the European Association of Neuro-Oncology and European Society of Medical Oncology (EANO-ESMO) LMD clinical practice guidelines recommend an individualized approached to patients with LMD that considers patient health status, performance status, histological and molecular subtype of the primary cancer, systemic therapy options, and overall radiographic burden of disease (7). In unfavourable patients (estimated life expectancy of <1 month), best supportive care is once again preferred.

Diagnosis

Establishing a clinical diagnosis of LMD based on history and physical exam alone is generally not possible given the variability and non-specificity of signs and symptoms. Therefore, imaging and CSF cytology remain the cornerstones of a complete work-up for LMD. Gadolinium-enhanced MRI is the best imaging modality for detecting LMD and should include both the brain and complete spine given that the entire neuraxis is at risk (1,11). The sensitivity and specificity of contrast-enhanced MRI in diagnosing LMD ranges from 70–85% and 75–90%, respectively (2,22,23). LMD may present as enhancement of the brain surface, cerebellar foliae, cerebral sulci, cranial nerves, and spinal nerve roots (24-26). Pathological enhancement may appear as nodular, linear, or curvilinear, and is described as either focal or diffuse intensification (27). Intradural extramedullary enhancing nodules in the subarachnoid space are common in disease involving the cauda equina

Table 1 Symptom management for patients with LMD

Symptom	Non-pharmacologic	Pharmacologic
Headache		Corticosteroids (e.g., dexamethasone 4–8 mg in morning and afternoon with food on severity of symptoms and extent of intracranial edema); additional analgesia may be required
Nausea/vomiting	Consume small frequent, bland, room temperature meals throughout the day to limit odour; If vomiting occurs, introduce sips of clear fluid first, then dry starchy food (e.g., toast), then protein rich food	Corticosteroids (e.g., dexamethasone 4–8 mg in morning and afternoon with food); Consider the addition of olanzapine if corticosteroids not sufficient
Fatigue	Maintain safe physical activity at lower levels of intensity (e.g., walking, home-based exercises) and within patient tolerance (12). Effective for improving cancer-related fatigue during and after treatment (13)	Limited evidence to support pharmacologic interventions for fatigue. The use of psychostimulants like methylphenidate is controversial and optimal dosing has not been established in this population (12,14)
Delirium	Maintain a quiet, well-lit, peaceful environment with a clock, calendar and familiar personal belongings visible to the patient (15,16) Correct reversible contributing factors: dehydration, nutrition, sleep deprivation (15,16)	Corticosteroids is helpful if delirium primarily from intracranial disease Haloperidol 0.5–1.0 mg oral or subcutaneous BID to TID
Sleep disturbance	Cognitive behavioral techniques including optimizing sleep hygiene, relaxation therapy, and stimulus control (17)	Short-acting benzodiazepines and zopiclone are helpful for sleep-onset insomnia; Intermediate-acting benzodiazepines are helpful for nocturnal awakenings Given the risk of addiction, hypnotic medications are generally recommended for short durations (<4 weeks) and used sparingly, 2–3 times a week oppose to every night. For patients with a limited survival this issue may be of less concern
Hiccups	Breath-holding, nasopharyngeal irritation (e.g., drinking water) (18)	Baclofen 10 mg TID 5 days has evidence of benefit in stroke patients (19) Metoclopramide 10 mg TID ×15 days has evidence of benefit in a mixed cancer population (20)

LMD, leptomeningeal disease; BID, twice daily; TID, three times daily.

and can be difficult to quantify given their small size and propensity to be adjoined by linear enhancement (11). Subependymal deposits and communicating hydrocephalus can also occur (7). Imaging should be completed prior to neurological procedures such as lumbar punctures, as they may cause inflammation or lower the ICP leading to extraneous enhancement and potential false positives (1,2). Conversely, a negative MRI does not exclude the presence of LMD, as 20–30% of patients with LMD have a normal MRI (28).

When possible, the CSF should be sampled in close anatomical proximity to clinical and radiographic evidence of disease (11). At least 10 mL of CSF should be acquired and processing should be completed soon after drawing the sample to maximize viability (9,11,29). Repeated CSF cytology is often required as the sensitivity following an initial lumbar puncture can be as low as 50%. With a second CSF sampling, this rises to approximately 75% (10,30). In patients with LMD, pleocytosis, hypoglycorrhachia, and elevated protein can be found in the CSF, with a raised opening pressure above 200 mmHg reported in 50–70% of positive patients (31). These CSF characteristics are not specific to the disease and infectious or inflammatory conditions may increase the rate of false positives. Flow cytometry can improve detection rates but is typically reserved for hematologic malignancies.

Meningeal biopsy is rarely indicated in the diagnosis of LMD; however, it may be considered in patients with a high clinical suspicion of LMD and localized radiographic findings, but a negative CSF cytology (32). In addition,

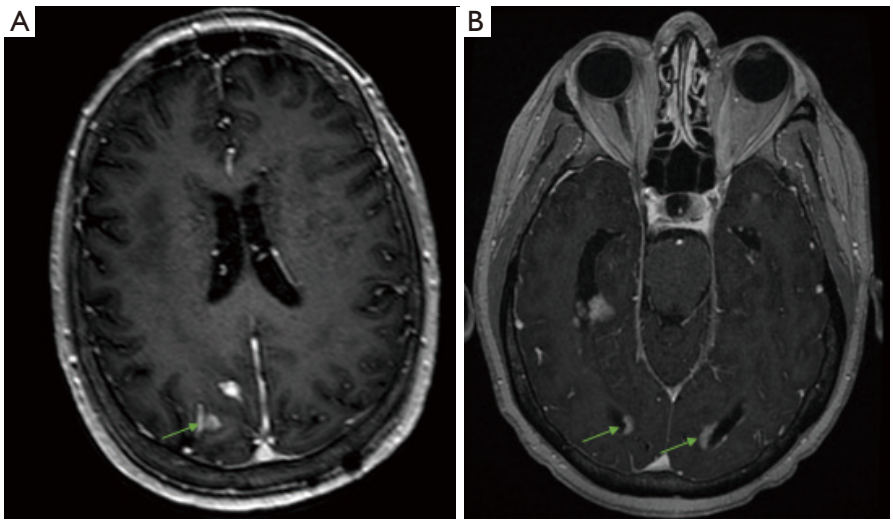

Figure 1 Axial gadolinium-enhanced MR brain imaging. (A) Focal classic LMD filling the cerebral sulci. (B) Nodular periventricular LMD. LMD, leptomeningeal disease.

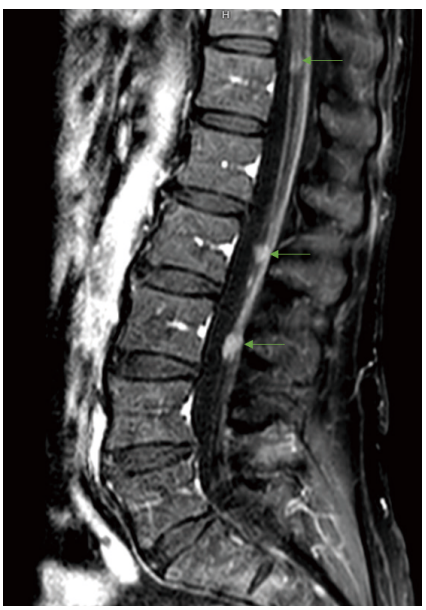

Figure 2 Sagittal gadolinium-enhanced MR spine imaging. Several enhancing nodules of LMD adherent to the cauda equina. LMD, leptomeningeal disease.

detection of tumor markers and circulating tumor cells (CTCs) in the CSF has been explored, but is still in its infancy with limited utility in conventional workup (33). Moving forward, these supplementary investigations may assist in the diagnosis of LMD, particularly in the setting of equivocal findings from imaging and CSF cytology.

CTC of circulating DNA (ctDNA) assays have also been studied as a means of detecting tumors cells in the CSF and potentially aiding in establishing a diagnosis of LMD. In one prospective study of 81 patients, the CTC assay examined demonstrated a sensitivity of 94% and specificity of 100% (34). Another group used a novel approach called rare cell capture technology to detect CTCs within the CSF and with this technique demonstrated a sensitivity and specificity for diagnosing LMD of 93% and 95%, respectively (35). At the 2020 American Society of Clinical Oncology meeting, a new platform was presented that was able to isolate CTCs from CSF in breast cancer patients in addition to detecting actionable mutations from nucleic material in the CSF (36). These results are promising diagnostic advancements for patients with LMD and further work is required to determine how to best integrate these techniques into clinical practice.

Prognosis

The overall prognosis for patients with LMD is poor, and without treatment the life expectancy for many is 4–8 weeks following diagnosis. With treatment, this can be extended to approximately 2–6 months depending on their response to treatment and underlying tumor histology (2,7,9,37). Early identification is essential, as patients with fewer neurological deficits and lower CNS burden generally

achieve improved treatment responses (11). Other favorable prognostic factors include a KPS >70, unimpaired CSF flow, and low CSF protein (<50 mg/dL) (1,38). Primary tumor histology and chemosensitivity also influence management. For example, LMD patients with breast or hematologic malignancies have demonstrated improved survival compared to other solid tumor primaries (11). In addition, the subtype and extent of LMD may have an impact on OS; however, this remains controversial and is further discussed in the Patterns of LMD section below.

Patterns of LMD

The intracranial meninges are membranous layers between the skull and brain and include the dura mater, arachnoid mater and pia mater. Two fused membranes comprise the dura mater which is also known as the pachymeninges. Pachymeningeal or dural-arachnoid enhancement is typically observed radiographically against the skull or along dural reflections. The remaining deep layers of the meninges, the arachnoid and pia mater, are collectively known as the leptomeninges. Leptomeningeal or pia-arachnoid enhancement can appear similarly to pachymeningeal enhancement along brain surfaces but may also affect the subarachnoid space and associated structures (11).

Patients may present with focal or diffuse disease on contrast-enhanced MR imaging of the brain and/or spine. There are variations in the radiographic appearance of LMD including linear/curvilinear enhancement, cranial nerve/nerve root enhancement, or nodular enhancement (27). Intracranial LMD tends to present along the cerebral convexities, cerebellar folia, basal cisterns and ventricular ependyma (*Figure 1*). Within the spine, all levels of the spinal cord are at risk, however LMD is commonly observed as enhancement and/or nodularity in the cauda equina (*Figure 2*).

The descriptor "bulky" has long been used to describe a radiographic appearance of LMD that potentially has both treatment and prognostic implications. Bulky LMD is commonly cited as an indication for radiotherapy given its propensity to cause symptoms, obstruct CSF flow and its similarity to parenchymal brain metastases where upfront radiotherapy is typically considered (37). Furthermore, intrathecal chemotherapy (ITC) has a limited penetrance of only 2–3 mm into brain and spine tissue, therefore, bulkier disease may be less responsive to this approach (39). Early reports have suggested that bulky LMD is a poor prognostic sign associated with worse survival (40,41); however, the overall burden of disease in patients with bulky LMD was not clearly reported in these studies.

In modern reports, the term nodular LMD has increasingly been used to acknowledge a distinct radiographic pattern of intracranial LMD that likely includes cases which may have previously been described as 'bulky' (7,42,43). Recently, a formal classification scheme was proposed by Turner *et al.* that identified two different radiographic patterns of LMD: classical LMD (cLMD) and a less consistently recognized nodular LMD (nLMD) (42). Patients with cLMD are described as having a pattern of enhancement that resembles "sugar coating" of the brain surface. Specifically, this may involve curvilinear or gyriform enhancement along the cerebellar folia, cerebral sulci, or cisterns and/or enhancement along cranial nerves without nodularity. In contrast, nLMD is characterized by focal enhancing nodules adherent to surfaces in contact with CSF including dural/pial surfaces, ventricles, tentorium or hypervascular dural tails. This classification is specific to intracranial LMD and does not address nodular spinal lesions.

Neuroimaging aside, there are other clinical features that may help differentiate between cLMD and nLMD. Several reports have observed a higher incidence of nLMD following surgical resection of brain metastases (44-46). Nguyen *et al.* reported a series of 320 intact or resected brain metastases treated with single-fraction stereotactic radiosurgery or hypofractionated stereotactic radiotherapy (SRT) (46). On multivariate analysis, resected metastases opposed to intact metastases were predictive of LMD and 73% of these patients developed nLMD. Similarly, Cagney *et al.* examined a large retrospective cohort of 1,188 patients who received resection and SRT or SRT alone for newly diagnosed brain metastases (44). They reported nLMD (which they termed pachymeningeal seeding) occurred in 36 of 318 patients who underwent surgery compared with no cases observed in 870 patients who received SRS alone. While pachymeningeal enhancement is anatomically distinct from leptomeningeal enhancement, the authors define pachymeningeal seeding as nodular, enhancing tumor stemming from the pachymeninges. Based on imaging alone, it is challenging to reliably differentiate between nodular pachymeningeal disease and nLMD, therefore our group considers these to refer to the same entity. The discrepancy in terminology highlights the need for standardization and in to that regard we endorse the framework proposed by Turner *et al.* Prabhu *et al.*

studied a cohort of 147 patients who developed LMD after surgical resection and post-operative SRT, differentiating as well between cLMD and nLMD. They observed that patients with cLMD were more likely to be symptomatic than those with nLMD (71% *vs.* 51%; P=0.01). Of particular interest, there was a median survival advantage for patients with nLMD compared with those who had cLMD (8.2 *vs.* 3.3 months; P<0.001). Multivariate analysis also reinforced nLMD as predictive of OS. Contrary to this finding, Nguyen *et al.* did not find any differences in survival between cLMD and nLMD. Further investigation is required to determine the prognostic implications of nLMD.

Radiotherapy

Patients with LMD will often receive cranial and/or spinal radiotherapy as part of their overall treatment. The indications for radiotherapy in this context include relief and/or stabilization of symptoms, nLMD or bulky LMD, relief for LMD-related CSF obstruction, and local control in highly selected patients with a low tumor burden (7,21,37). Radiotherapy is generally delivered using conventional palliative dose fractionation schedules (cRT) and approaches can range from focal brain/spinal radiotherapy (FRT) to whole brain radiotherapy (WBRT) to craniospinal irradiation (CSI). There is no level I evidence to guide radiotherapy approaches and much of the evidence supporting its use is based on retrospective, observational studies and expert opinion. To this point, a recent systematic review identified 18 retrospective studies that have suggested a survival benefit with the inclusion of radiotherapy in treatment regimens for patients with LMD (37). A summary of select radiotherapy studies are summarized in *Table 2*.

WBRT

Specific to WBRT, multiple retrospective studies report that its addition is a predictor of improved survival in patients with LMD from varying histologies (47,48,50,54,55). Three of these studies looked explicitly at the outcomes of WBRT alone and the median OS in these series ranged from 2 to 6 months (47,48,54). The largest of these was a study of 206 patients with intracranial metastases (120 with LMD) from various primary histologies. Unfortunately, few patients were assessed post-radiotherapy for radiographic improvement. Of 15 patients who completed cranial MR imaging after radiotherapy, a complete response was observed in 4 patients, a partial response in 7 patients and stable disease in 3 patients. Progression of disease was only observed in one patient (47). Ozdemir *et al.* reported a retrospective cohort of 51 patients with intracranial LMD from non-small cell lung cancer (NSCLC) who received WBRT, either 30 Gy in 10 fractions (30 Gy/10) or 20 Gy in 5 fractions (20 Gy/5). Radiographic response was poor with only 24% of patients demonstrating improvement or stability on post-treatment MRI, but symptomatic improvement was more favorable and observed in 84% of patients (48). Factors predictive of improved survival following WBRT include a favorable performance status (ECOG 0-1), longer time between primary diagnosis and development of LMD (>11 months), asymptomatic patients, and an absence of parenchymal brain metastases at presentation (47,48).

Common palliative WBRT dose fractionation schedules include 20 Gy/5 or 30 Gy/10 delivered daily, 5 days a week. Other longer schedules (e.g., 37.5 Gy/15, 40 Gy/20) may occasionally be used at certain institutions; however, shorter courses should be considered in patients with a limited life expectancy. WBRT is delivered using two lateral opposing radiation fields directed at the cranium. The superior, posterior and anterior field borders are placed to clear the skull by at least 2 cm. The inferior margin is typically placed at the C2/C3 intervertebral space (56). Customized shielding is generated to prevent unnecessary irradiation of the patient's oropharynx and bilateral lenses. Particular care should be taken in ensuring all brain tissue and CSF spaces (including the posterior orbital spaces, basal cisterns and lamina cribrosa) are well covered within treatment fields. The acute toxicities associated with WBRT include fatigue, alopecia, headache, nausea/vomiting, otitis media, scalp dermatitis, xerostomia, and taste changes which may develop during radiotherapy or shortly after its completion. Acute toxicities typically resolve within days to weeks following radiotherapy and the temporary use of dexamethasone and antiemetics may be used to manage symptoms. Late toxicities include persistent fatigue, cognitive dysfunction, cerebrovascular effects, and pituitary dysfunction.

FRT

FRT may be considered in patients with localized nLMD, bulky spinal disease, and/or to relieve CSF obstruction (2,21,37,56,57). Restoring CSF flow may improve hydrocephalus, alleviate symptoms, and facilitate

Table 2 Summary of select retrospective radiotherapy studies in patients with LMD

Author	Patients (N)	Histology	% patients receiving treatment	Median survival (months)	Key findings
Sakaguchi (47)	206	Mixed	100% WBRT; 8% surgery	6	Of 15 LMD patients with post-radiation MRI: 4 CR, 7 PR, 1 progressed
Ozdemir (48)	51	NSCLC	100% WBRT	3.9	Benefit with WBRT if favorable performance status
Milgrom (49)	44	Lymphoma/leukemia	95% WBRT; 70% chemotherapy; 2% CSI	7	MRI response post-radiation: 42% CR, 46% PR
Liao (50)	212	NSCLC	60% WBRT 58% targeted therapy	4.5	WBRT, targeted therapy and chemotherapy were all independent predictors of improved survival.
Niwinska (51)	149	Breast	62% radiotherapy; 65% ITC; 52% chemotherapy	4.2	Statistically significant difference in median survival between patients who had radiotherapy and those who did not (P=0.028)
Morris (52)	125	NSCLC	45% WBRT; 30% BSC; 16% chemotherapy; 15% targeted therapy	3	No difference in survival noted between patients who received WBRT and those who did not
Hermann (53)	16	Mixed	100% CSI	3	68% had an improvement in symptoms after radiotherapy

NSCLC, non-small cell lung cancer; WBRT, whole brain radiotherapy; CSI, craniospinal irradiation; CR, complete response; PR, partial response.

further treatment if intrathecal chemotherapy (ITC) is a consideration. Radiotherapy has been reported to alleviate CSF obstructions due to LMD in 50% of intracranial cases and 30% of spinal cases (58). For patients with nLMD or bulky spinal disease, localized conventional radiotherapy to the involved site may be offered to both symptomatic or asymptomatic patients. In well-selected cases of intracranial nLMD, focal SRT may also be considered and has been reported in recent studies (44,45). In the cohort from Prabhu *et al.*, there were 71 patients who received salvage WBRT or FRT after developing nLMD. Patients who received FRT (either SRT or conventionally fractionated partial brain radiotherapy) had a significantly longer median OS versus patients who received salvage WBRT (13.3 *vs.* 6.6 months; P<0.001). There is likely an underlying selection bias as patients who received FRT presumably had localized, smaller volume disease. Nonetheless, these findings suggest that with careful patient selection, prolonged survival is possible in patients with LMD.

If conventional FRT is delivered, dose fractionation schedules would typically be the same as those for WBRT. With SRT, common dose schedules include 15–20 Gy in 1 fraction, 27 Gy in 3 fractions and 25–35 Gy in 5 fractions delivered daily or every other day. SRT can be adequately delivered by multiple different treatment platforms including linear accelerators, CyberKnife, or Gammaknife depending on institutional resources. Acute toxicities associated with SRT depend on the intracranial site being irradiated but may include fatigue, headache, nausea/vomiting, and worsening of any presenting neurological symptoms. The most significant late toxicity is radiation necrosis (RN), which typically develops several months from completion of SRT. Pathologically-proven RN rates are as low as 4.2% at 1 year (59), while imaging-based RN rates are upwards of 10–15%, although only a subset are typically symptomatic (60,61).

CSI

CSI with conventional photon radiotherapy is generally avoided in the setting of LMD given the potentially significant toxicity profile, the palliative intent of treatment, and the lack of evidence for a survival benefit. In highly selected patients, however, this may be reasonable approach

to consider. El Shafie *et al.* reported a single institution retrospective series of 25 patients who received palliative CSI for LMD, 72% of whom had associated parenchymal brain metastases as well (62). Treatment was delivered using a conformal helical intensity-modulated radiotherapy (IMRT) technique and the most common dose prescribed was 36 Gy/20. The median OS for all patients was 19 weeks and factors that demonstrated a statistically significant improvement in survival included younger age, better KPS, and neurologic response to treatment. In patients with a KPS ≥70 (n=15), the median OS was 28 weeks compared with only 9 weeks if the KPS was <70. CSI led to stabilization or improvement in intracranial pressure-related symptoms in nearly all patients (presumably the WBRT component) and stabilization or improvement in motor or sensory symptoms in 68% of patients. The most common toxicities were grade I-II fatigue (84%), grade III myelosuppression (32%), and grade I-II nausea (36%). In patients who developed myelosuppression, 6 did not proceed to receive systemic therapy due to poor performance status, which the authors indicated was not directly related to the hematologic toxicity.

Proton-based CSI is an intriguing option for patients who may be suitable candidates for CSI at centres with the capabilities for proton therapy. To our knowledge, there are no peer-reviewed publications investigating this proton CSI in the context of LMD; however, there is promising evidence for its use in patients with primary medulloblastoma.

Systemic therapy

Intrathecal therapy (ITT)

ITT is an intuitive means of administering systemic treatment directly into CSF spaces in the setting of LMD. Assuming CSF flow is not inhibited, ITT allows distribution of the drug to the entire neuraxis, bypassing the blood-brain barrier and achieving therapeutic levels in the CSF while limiting systemic toxicity (2,11). ITT can be administered through repeated lumbar puncture or an implanted intraventricular catheter system. The advantage of the intraventricular method is that it ensures the drug is delivered correctly to the subarachnoid space rather than the epidural or subdural regions. Furthermore, it provides a more uniform distribution allowing drugs with a short half-life to be used effectively, as well as being more comfortable procedure for the patients, which increases compliance (7).

Methotraxate, thiotepa and cytarabine are all commonly used agents for ITT. Methotrexate is typically administered twice a week, usually with folinic acid, while thiotepa is given 2–3 times per week as a bolus (63,64). Liposomal cytarabine is preferred over free cytarabine given its increased efficacy, simplicity, and extended CSF half-life, allowing administration every 2 weeks (65). For treatment of LMD, however, the optimal agent, dosing, and schedule has not yet been clearly defined (2). None of these therapies have shown any advantage over the other, and combined treatment has not proven to be more effective than single agent therapy (66-68).

There are several limitations that restrict the widespread use of ITT for LMD. As mentioned, ITT only penetrates 2–3 mm into spine or brain tissue, restricting its utility to patients with only linear enhancement on imaging as opposed to nodular and bulky disease, as well as significant CSF tumor cell load (7,69). In addition, if CSF flow is obstructed, agents may not infuse to areas of concern and backlog can lead to undesirable neurotoxicity (1). With intraventricular ITT, aseptic chemical meningitis can occur and presents with signs and symptoms of a typical meningitis, but can be more significant if there is CSF flow obstruction (11,70). It usually resolves in 5 days from administration of ITT and can be treated with a short course of oral corticosteroids. Leukoencephalopathy can also occur and its presentation may range from mild neurological symptoms to severe impairments such as motor dysfunction and aphasia (70). The risk depends on the dose of methotrexate administered and whether they received radiotherapy. Myelosuppression and myelopathy are possible related systemic effects of ITT, with paraplegia rarely being reported (11).

There is a paucity of evidence supporting the use of ITT in LMD, and there is no consensus on a standard treatment protocol. Boogerd *et al.* examined 35 breast cancer patients with LMD randomized to ITT or standard therapy alone (71). There was no difference in survival, but accrual was poor and patient characteristics were not well balanced. Bokstein *et al.* studied 104 patients with LMD from solid tumors, comparing the addition of ITT to RT and systemic chemotherapy alone (72). Response rates were 86% with ITT versus 74% without, which was not statistically significant, and no difference in survival was observed between the cohorts either. With limited and heterogeneous prospective data, the decision to use ITT in LMD is mostly guided by expert opinion (73). Several upcoming randomized trials will help to define the role of

ITT in the general LMD population.

Targeted therapy

In patients with HER-2 positive breast cancer and previously untreated brain metastases, the combination of lapatinib and capecitabine has shown promising results in the single-arm phase II LANDSCAPE trial (74). Forty-five patients without previous WBRT were enrolled in this trial and a partial CNS response was observed in 66% of these patients. In breast cancer patients with brain metastases. the novel agent trastuzumab emtansine (T-DM1) may have CNS activity, although the data remain limited. T-DM1 is an antibody-drug conjugate comprised of the monoclonal antibody trastuzumab and the cytotoxic agent DM1 (75). The KAMILLA study was a single-arm phase IIIb safety study of T-DM1 for patients with HER2-postive breast cancer who progressed after previous chemotherapy and a HER2-targeted agent. In an exploratory subgroup analysis of this trial, 399 patients with stable baseline brain metastases were examined (76). Out of 126 patients who had measurable brain metastases, a radiographic decrease in the size of target brain lesions was observed in 84 (67%) patients. A multi-institutional retrospective study included 39 breast cancer patients with brain metastases treated with T-DM1 (77). The majority of patients also received WBRT. A median 8 cycles of T-DM1 were administered with reasonable toxicities and a median PFS of 6.1 months.

Approximately 15% of patients with lung adenocarcinoma have epidermal growth factor receptor (EGFR) mutations and may be eligible for targeted tyrosine kinase inhibitors (TKIs). First-generation EGFR TKIs include erlotinib and gefitinib, and while their CNS penetrance is poor, high-doses may overcome this barrier and allow for therapeutic concentrations in the CSF (60). Osimertinib is a novel third generation TKI with promising results from a recent phase I trial for patients with metastatic NSCLC and LMD (78). In this trial, 41 patients were enrolled and the RANO LMD response assessment criteria were used. The overall objective response rate was 41% and the median duration or response was 8.3 months. In addition, CSF tumor cell clearance was observed in 28% patients. Another novel EGFR TKI is AZD3759, which has demonstrated exceptional CNS penetration of the blood-brain barrier (79). Currently the data remains limited in its effectiveness in treating CNS disease, including LMD (80). Anaplastic lymphoma kinase (ALK) rearrangements are another potential target in NSCLC, and TKIs specific for the ALK fusion oncogene may be a viable treatment option. For patients with CNS involvement, there is evidence to suggest that second-generation ALK TKIs such as alectinib and ceritinib have improved BBB penetration compared to first-generation agents such as crizotinib (Wang). Ceritinib following pulse-dose crizotinib was found to have durable control of brain metastases and LMD in an ALK-positive patient whose brain lesions were unsuccessfully treated with the standard crizotinib (75). Moving forward, the ASCEND-7 study (NCT02336451) is investigating ceritinib in ALK-positive NSCLC patients with brain metastases or LMD. Results showed ceritinib had an overall intracranial response rate of 51.5% in patients with ALK-positive NSCLC patients with no prior brain radiotherapy or ALK targeted therapy.

Immunotherapy

With the rapid adoption of immune checkpoint inhibitors for multiple different primary malignancies, there has also been interest in its application for patients with LMD. Programmed cell death 1 or programmed cell death ligand 1 (PD-1/PD-L1) inhibitors have substantially changed treatment pathways in metastatic disease, and their potential impact on disease progression in LMD is promising. While agents such as nivolumab and pembrolizumab have higher molecular weights which restrict their penetration into the blood-brain barrier, innate and adaptive immune cells may still permeate into the CSF and have a therapeutic effect (2). Furthermore, other interfaces such as the choroid plexus may provide alternative means of entry into the CNS, allowing access to tumour-infiltrating lymphocytes and PD-L1 expression (81,82).

At this time, immune checkpoint inhibitors have demonstrated efficacy in the treatment of patients with brain metastases (83-85). However, data for LMD are limited and several trials are currently underway to investigate the utility of these agents. Brastianos *et al.* are conducting a phase II trial of pembrolizumab in LMD from any solid tumour malignancy (NCT02886585). The interim analysis reported 44% of patients were alive at 3 months, demonstrating an overall survival benefit comparable to historical controls, with a toxicity profile similar to the non-LMD population. In addition, a phase I study examining Avelumab combined with WBRT is currently accruing for all disease sites (NCT03719768). For patients with LMD from metastatic melanoma, the combination of ipilimumab and nivolumab is being investigated (NCT02939300),

as well as intrathecal nivolumab (NCT03025256). The forthcoming results from these trials may provide clarity to the role of immunotherapy in LMD.

Response assessment

Following treatment for LMD, the components of a comprehensive response assessment include neurological assessment, CNS imaging and, when applicable, CSF cytology/flow cytometry (1,2). The Response Assessment in Neuro-Oncology (RANO) working group proposed a clinical tool consisting of 10 domains to be evaluated in a standardized neurological assessment (27). This includes components such as gait, strength, sensation, vision, hearing, level of consciousness, and behaviour. Each of these domains are scored on a scale from 0 (normal) to 2–3 (dysfunction), with progressive disease defined as a change of 2 or more in a given domain, or change to the highest level in any one domain. While clinical improvement in symptoms would be ideal, it is important to recognize that many of the neurological deficits caused by LMD are irreversible, and in many cases the primary treatment objective may be to preserve current function and delay deterioration rather than achieving a complete resolution. Furthermore, symptoms of LMD may be confounded by separate parenchymal brain metastases, systemic progression, and medication/treatment effects.

CSF cytology is an important consideration in the workup of patients with LMD, particularly those with hematologic malignancies or CNS lymphoma. In patients with solid tumor malignancies, CSF assessment may not always be feasible and in many cases a working diagnosis can be established based on the clinical presentation and neuroimaging assuming typical findings are observed. RANO defines complete CSF response as the conversion of cytology from positive to negative at all sites of known disease and is sustained for at least one month (27). Progressive disease is defined as CSF shifting from negative to positive cytology, or a failure to convert to negative following therapy. Overall, CSF cytology as a response marker is limited by its poor sensitivity and nuances in obtaining and processing the sample as previously described (11). Additionally, it is unclear how to interpret positive cytology results in the setting of clinical and radiographic stability.

Neuroimaging is a vital yet challenging component of the response evaluation process. The radiographic assessment of LMD can be complicated by non-specific patterns of enhancement that are suggestive but not definitive for LMD as well as variability in slice thickness and image acquisition, which presents particular difficulty with smaller lesions (2,27). In addition, though not considered in the radiological assessment of LMD, changes in parenchymal brain or spine metastases should still be described as per protocol. If MRI and CSF are assessed at the same timepoints, MRI should precede lumbar puncture to avoid imaging artifact. Currently, there is not a defined role for other neuroimaging modalities, such as MR spectroscopy, MR perfusion, or positron emission tomography (PET) (7).

The RANO working group has proposed a scoring system for radiological evaluation, which assesses 6 regions of the CNS for pathological contrast enhancement (27). These findings are categorized as present, absent, or non-evaluable. Target nodules are reported as definitely worse if the sum of product of the baseline orthogonal diameters is increased by 25%. Partial response is defined by a 50% or greater decrease in the summed product of orthogonal diameters. The RANO radiological scoring system was recently assessed by several neuroradiologists but unfortunately did not achieve adequate interobserver agreement, suggesting the system may not yet be effective for clinical practice (86). An updated scorecard was proposed, reducing the CNS sites of interest, and simplifying instructions, with plans to undertake validation prior to implementation into practice. Despite these efforts, imaging response evaluation remains challenging, and warrants the involvement of specialized neuroradiologists with central imaging review when necessary.

Conclusions

LMD is a challenging diagnosis for cancer patients that is associated with morbidity and a poor prognosis. We recommend a multidisciplinary approach to the care of these patients that includes neuroradiologists, medical oncologists and radiation oncologists. There is a need for standardization in the interpretation and reporting of the radiographic features of LMD and response assessment after treatment both in clinical practice and on trials. For patients with LMD, radiotherapy (including WBRT, focal spinal radiotherapy or CSI) and chemotherapy have been the mainstays of palliative treatment for patients with LMD. While outcomes following treatment remain poor, the emerging role of novel systemic agents and SRT in carefully selected patients are promising and in need of further study.

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