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Leptomeningeal Metastases and Intrathecal Chemotherapy

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Abstract

Leptomeningeal metastases (LM) is a rare but devastating complication of advanced cancer. Advances in cancer treatment has markedly improved the survival, nonetheless, due to the poor penetration of these treatments beyond the blood-brain and blood-CSF barrier for most modalities, creating a sanctuary site in the CNS/CSF space for the disease, and reflecting as increased incidence of LM. Whereas the goal of LM treatment remains to be symptom palliation and not elongation of survival, the optimal treatment, and whom to treat remains to be somewhat controversial. Herein we review the advances in LM treatment focusing on the role of intrathecal chemotherapy.

Keywords: leptomeningeal metastases, intrathecal chemotherapy, prognosis, diagnosis, assessment

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1. Introduction

Leptomeningeal metastases (LM) from cancer was first described in 1870 [1], erstwhile described as a rare complication, and now a common complication among patients with advanced solid tumors [2–12]. Clinical trials are few and are negative or inconclusive, partly because many patients with LM are poor candidates for trials due to low-performance status and rapid clinical decline.

The diagnosis of LM is challenging and remains unclear in many cases, and the disease is not measurable in many cases. The CSF and CNS are protected by the blood-CSF, and blood-brain barriers (BBB) which makes it hard for systemic agents to reach the target. Penetration of intrathecal treatments into the disease limits the efficacy of treatment. Furthermore, and obviously, LM is not one disease but derives from many primary cancers, some of which have several molecular subtypes. This

background is at least part of the reason that the prognosis of LM remains devastating with an average survival of 2 to 4 months regardless of the type of treatment.

Here, we review solid tumor derived LM with some emphasis on intrathecal chemotherapy.

2. Epidemiology

LM is present at the time of initial intracranial involvement in 2%–12% of cancer patients and based on prospective studies, can also develop later in the clinical course in 1%–37% of patients [6, 13]. Coexisting brain metastases are present in 50–80% of patients [14–17] and more than 80% have extra-cranial metastases. This incidence could be underestimated due to the difficulty of LM diagnosis and the relatively high frequency of false-negative results [18].

The common solid tumors that give rise to LM somewhat mirrors that of brain metastases, the most common being breast cancer (12–35%) followed by lung cancer (10–26%), melanoma (5–25%), gastrointestinal malignancies (4–14%) and cancers of unknown primary (1–7%) [10, 14, 19–22].

It is important to distinguish LM from postsurgical pachymeningeal seeding, a phenomenon which complicates approximately 8% of resections for brain metastases and of which is increasing in an era of whole brain therapy omission, and generally associated with a significantly better prognosis than true LM [23–25].

The incidence of LM continues to rise not only as a result in advances of systemic therapy but is also assumed that advances regarding the precision of diagnostic imaging contributes to the climbing overall incidence.

2.1. Breast cancer

The incidence of LM in breast cancer is rising as patients live longer with the improvement of systemic therapy [18, 20, 26]. LM is present at the time of intracranial involvement in approximately 10%–12% of patients with breast cancer and develops in up to one-third of patients thereafter [3, 5–7, 9].

A predisposition to LM of lobular histological type is well established. Whereas the overall incidence of intracranial involvement of lobular carcinoma is approximately 35%, the rate of parenchymal brain metastasis in lobular carcinoma is only about 7%, suggesting a high propensity for leptomeningeal dissemination of this subtype [27, 28]. Autopsy data of metastatic breast cancer patients revealed an incidence of LM in invasive lobular breast carcinoma of 14% compared with 1% of invasive ductal breast carcinoma [29, 30].

The proportion of LM with breast cancer also differs according to molecular subtypes: approximately 40% of LM are related to the triple-negative subtype. LM presents as a late-stage complication of breast cancer and is diagnosed in patients with active and progressive systemic disease in up to 70% of cases [31] with a median interval of time from diagnosis ranging 2 and 7 years [32, 33]. LC in triple-negative disease develops after a significantly shorter time from the diagnosis of breast cancer than other subtypes.

Although Human Epidermal Growth Factor Receptor 2 (HER2) positive disease is known to have a propensity to metastasize to the CNS, this association is not directly translated to LM. Retrospective data shows that HER2-positive disease is less frequent than luminal and triple-negative subtypes accounting for approximately 10–15% of the cases [27, 34, 35]. A 14% prevalence of concurrent LM at the time of brain metastasis diagnosis has been reported in a HER2-positive breast cancer cohort [33].

The molecular status concordance rate between metastatic breast cancer cells in CSF and primary tissue is known to be very high [36], especially in the HER2 subtype (up to 95%) [34].

The development of LM may also be influenced by the choice of chemotherapy. For instance, molecular targeting agents including monoclonal antibodies that can induce tumor dormancy dramatically such as trastuzuamb in HER2 positive breast cancer, fail to penetrate the intact BBB and B-CSF-B, and allow growth to malignant cells that are shielded from these agents [7, 37–40].

2.2. Lung cancer

Non-small cell lung cancer (NSCLC) harbors a potential for leptomeningeal dissemination with approximately 2% of patients displaying LM at diagnosis of intracranial involvement. Thereafter, the cumulative incidence of LM increases with time, particularly among patients with Anaplastic Lymphoma Kinase (ALK) rearrangements or EGFR mutations [41].

A prospective study of 458 newly diagnosed small cell lung cancer (SCLC) indicated a 2% incidence of LM at the time of diagnosis, and a 2-year cumulative incidence of 10% [42].

3. Diagnosis

The diagnosis of LM is based on clinical evaluation, cerebrospinal MRI and cerebrospinal fluid (CSF) analysis. According to the European Association of Neuro-Oncology-European Society of Medical Oncology (EANO-ESMO) guidelines, the diagnosis of LM is confirmed by detection of tumor cells in the CSF, probable or

possible in the presence of typical clinical imaging signs [18]. The combination of these three items leads to the diagnosis of LM type I when the CSF cytology is positive, or LM type II (probable/possible) with typical MRI characteristics and neurological signs. Based on the MRI pattern, LM may be further partitioned as linear (subtype A), nodular (subtype B), linear and nodular (subtype C) or hydrocephalus (subtype D).

3.1. Clinical features

LM presents with protean manifestations. Symptoms are most often attributable to meningeal irritation, intracranial hypertension, cranial and spinal nerve dysfunction. Symptoms develop over several days to weeks, often presenting with multifocal neurological deficits, therefore making the clinical presentation non-specific [10, 43]. General symptoms such as headaches, nausea, vomiting, changes in mental status are symptoms that acquiesce LM to be underdiagnosed. Spinal signs such as limb weakness, dermatomal sensory loss are also signs that are overlooked, more recognizable when accompanied by severe vesicourethral disorder [44].

The location of these signs and symptoms can be divided into three anatomic compartments: cerebral hemispheres, posterior fossa/cranial nerves, and the spinal cord/nerve roots. 34% of patients present with symptoms localized to one compartment (cerebral, posterior fossa, or spine), 39% to two, and 25% to all three [43].

In a series of 150 patients with solid tumor LM, the most common presenting signs and symptoms were headache (39%), followed by nausea/vomiting (25%), leg weakness (21%), cerebellar dysfunction (17%), altered mental status (16%), diplopia (14%), and facial weakness (13%) [14, 43].

3.2. CSF studies

Routine studies on lumbar puncture includes opening pressure, cell count, glucose and protein concentration. The classical findings of LM are high protein concentration and low glucose concentration, lymphocytic pleocytosis, and positive cytology for malignant cells [10]. Elevation of opening pressure higher than 20 cm H_2O is suggestive but not diagnostic of LM [14]. The CSF protein concentration is elevated (>38 mg/dL) in 60–80% of cases as a result of BBB breakdown, although tumor protein production might contribute as well (from UpToDate). The CSF glucose concentration is decreased (CSF/serum ratio <0.6) in 30% of cases due to increased metabolism of the tumor itself as well as reactive pia, lymphocytes [10, 43].

The definitive diagnostic finding for LM is the cytological identification of a malignant cell within the CSF. CSF cytology is accurate in 54% of the time with a

single specimen and can remain false negative in 14% of patients even after 3 samples [12, 45]. Immunohistochemical staining of cells in the cytologic specimen may provide diagnostic information [46].

CSF tumor marker quantification can aid the diagnosis. Concentration of CSF tumor markers (eg, CEA, CA 15–3, CA-125) higher than 2–3% of simultaneous serum values are unlikely to be serum contamination, and rather a result of LM itself [46–48]. Concentrations higher than the serum value is almost certain of LM, even when the cytology remains negative. CSF tumor marker concentration can also be utilized to evaluate the treatment response quantitatively but requires precaution because the CSF sample might not represent the whole distribution of the disease within the CNS when a CSF blockade is present.

Admittedly, in this MRI era, LP is not always necessary. However, as mentioned earlier, even a small amount of CSF sampling may resolve the patient's symptoms transiently as a result of recovery from intracranial hypertension and meningeal irritation, already highly suggestive of LM. Repeated lumbar punctures are not realistic in the clinics, and motivate both the clinician and patient towards surgical intervention, i.e., implantation of a ventricular device such as an Ommaya reservoir.

3.3. Imaging studies

MRI abnormalities of LM include enhancement of the surface of the brain or spinal cord identified as enhancement of the cranial nerves and spinal nerve roots, brain surface, cerebellar foliae, and within cerebral sulci [49]. The abnormal enhancement may be nodular, linear, or curvilinear as well as focal or diffuse [50].

Multiple methods to better assess LM by imaging have been reported such as separate high-resolution contrast-enhanced skull base MRI to highlight subtle enhancement of the cranial nerves not appreciated on routine sequences, but still, not sufficient to aid inter-observer variability [51].

Experience with this proposed strategy and advances in technology—for example, postcontrast T2-FLAIR MRI—are likely to refine and improve neuroimaging assessment of LM in the future [52].

Spinal Gd studies should always be considered as spinal lesions tend not to be complained of, or asymptomatic and can be under diagnosed [49]. Bone metastases of the vertebras can be an obstacle for a lumbar puncture and should be checked prior to study [49].

The versatility of CT scan is indispensable in terms of preserving time for the diagnostic procedure, particularly in order to detect bulky lesions and/or LM complicated with hydrocephalus. CT scans do not yield definitive diagnosis of LM, nonetheless, can rule out situations unsuitable for lumbar punctures such as

obstructive hydrocephalus or large intracranial masses which might risk herniation. CSF sampling and cytology followed by the CT scan will not only allow for the definitive diagnosis of LM, but even a small amount of CSF withdrawal infrequently allows for rapid resolution of symptoms, which is already highly suggestive of intracranial pressure elevation, and indicative of LM. Consequently, this will allow the rapid decision making of immediate initiation of the treatment procedure, something indispensable in the face of this rapidly deteriorating complication.

There is no doubt that the gold standard imaging modality for LM diagnosis is a contrast enhanced MRI, but the procedure might be a burden for patients that are baffling from LM symptoms, and its omission is not infrequent.

4. Prognosis

Performance status at diagnosis of LM diagnosis, clinical, magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) cytology presentations, tumor histology and molecular subtypes are important prognostic factors [53–56]. Other factors include the protein level in the CSF at diagnosis, the administration of systemic or intrathecal pharmacotherapy, and initial response to treatment [56].

The EANO-ESMO group retrospectively reviewed 254 LM patients from solid tumors using the aforementioned guidelines reporting a remarkable prognostic value in predicting OS using this guideline [57].

- Younger age predicts better survival (P = 0.022).
- Positive cytology is a negative predictor of survival (median, 2.3 vs 3.5 months, P = 0.002).
- With positive cytology, nodular vs non-nodular MRI findings are predictive of survival (median, 2.7 vs 5.0 months, P = 0.014).
- For the common primary tumor types, the survival varies by tumor type (medians for type I and type II, breast, 2.4 and 4.5 months; lung, 2 and 2.9 months; and melanoma, 1.5 months and 2.2 months, respectively, P = 0.018).
- Systemic treatment correlates with better survival (P = 0.001 in the entire group). Subgroup analysis revealed better survival with systemic treatment in type I (HR = 0.58, P = 0.0004), confirmed in multivariate analysis, but not in type II (P = 0.46).
- Intrathecal treatment did not correlate with better survival in the entire group, but subgroup analysis disclosed better survival with intrathecal treatment in type I (HR = 0.70, P = 0.018), confirmed in multivariate analysis, but not in type II (P = 0.56).

Although this still needs to be explored in bigger datasets and prospective trials, the EANO-ESMO LM classification is highly prognostic and has been recommended for stratification and design of clinical trials [58].

Histology and molecular subtypes are also important factors that influence the prognosis. In a large series of 318 patients with breast cancer derived LM, median overall survival was 3.5 months for the entire cohort. Survival was longest among the HER2-positive, shortest for those with triple-negative disease (5.2 versus 2.5 months) [59]. Similarly, in NSCLC patients with LM from epidermal growth factor receptor (EGFR)-mutant or anaplastic lymphoma kinase (ALK)-rearranged tumors have the potential for more extended survival (eg, 12 to 18 months) compared with patients without a driver mutation [60–64].

The primary goal of LM treatment currently is to obtain neurological symptom relief, but recent studies show the importance of systemic treatment in order to retain general tumor dormancy. The overall survival of cancer patients with CNS metastases tends to depend on the existence of extracranial disease. According to the Japanese brain tumor registry 2005–2008 [65], the cause of death is deterioration of the extracranial disease (50–70%), and not CNS disease (20–40%) and therefore, overall survival is not a reliable read-out for treatment evaluation, but remains as an important factor.

5. *Treatment*

Patients with LM are at risk for rapid deterioration. Patients often require multidisciplinary care to achieve optimal symptom control and quality of life. Careful and comprehensive evaluation and rapid induction of treatment is of priority. The natural history of central nervous system (CNS) metastases is evolving with improvements in systemic cancer therapies, particularly for certain cancer subtypes and this stands true for LM as well. Prolonged survival is occasionally achieved, and selected patients with LM have a wider range of treatment options available to them. Alleviation of neurological status, life expectancy, and QOL is to be balanced with any side effect of the attempted treatment. Best supportive care is always a reasonable option.

5.1. Local therapies

5.1.1. Radiation therapy

Radiation therapy allows for resolve of CSF flow, rapid alleviation of symptoms, both which cannot be achieved rapidly by systemic treatment. It is an option that must be prioritized particularly to target bulky lesions [18, 66].

In the clinics, radiation therapy is frequently employed in the form of whole-brain irradiation (WBRT). It may be considered for extensive nodular or

symptomatic linear LM or co-existing brain metastasis. Yet, no association of WBRT with survival has been observed in retrospective studies [17, 27, 67–69]. To achieve symptom palliation and preserve neurologic function, this is often combined with focal RT of symptomatic spinal lesions [66, 70].

Typically, WBRT involves the skull base, cisterns, with the inclusion of the upper two cervical vertebrae scheduled as 30 Gy in 10 daily fractions: for poor-prognosis patients, 20 Gy in five daily fractions is sometimes used to minimize patient burden and treatment time [71]. However, WBRT can result in cognitive decline, which typically takes months or even years to become clinically apparent. Obviously, many patients do not live long enough to suffer the delayed effects of RT, but, some do.

Historically, craniospinal irradiation (CSI) was considered inappropriate for solid tumor LM due to two major reasons: the concern for acute side effects, particularly hematological toxicities, and technically difficult treatment application [18, 72, 73]. Nonetheless, CSI can be applied with promising results and favorable toxicity profiles with utilization of modern radiotherapy techniques such as helical Tomotherapy (HT) or Proton therapy [74–78], but both currently still lack versatility as a modality.

WBRT and concurrent systemic/intrathecal chemotherapy should be avoided because of the elevated risk of neurotoxicity. On the contrary, conformal radiation modalities including stereotactic radiotherapy is, theoretically, not contra-indicative, and can be an optimal treatment option [79].

Current ESMO guidelines recommend consideration of focal RT for circumscribed, symptomatic lesions and WBRT for extensive nodular or symptomatic linear LM [57]. WBRT is not recommended in the NCCN guidelines [66].

5.1.2. Intrathecal chemotherapy

Intrathecal injection of agents detour the BBB, B-CSF-B and allow direct delivery of the drug into the CSF with less systemic toxicity [80, 81]. Direct injection of different agents to this therapeutic location (CSF) in attempt to confer LM started in the early 1970's [80]. Several important trials were designed and conducted 10–20 years ago, however, with little statistical power, without challenging the concept of intrathecal chemotherapy, and criticized for methodological limitations. Most importantly these studies have included patients with LM from different primary tumors which cannot be considered state of the art today [53, 55, 82–84]. Thus, the role of intrathecal chemotherapy in LM from solid cancers remain unproven. Nevertheless, usage of intrathecal injections continue to be widespread [81, table 1].

Agents can either be injected directly into the lateral ventricle through a subcutaneous reservoir and ventricular catheter (i.e., an Ommaya device) or into

the lumbar sac by lumbar puncture (LP). Multiple reports clearly indicate that ventricular administration, and not LP, is the preferred choice unless the patient is unsuitable for surgical placement of a reservoir [18, 85–88]. Ventricular administration generally results in better distribution and avoids the approximately 10% risk that LP injections do not enter the CSF space [80, 89]. Intraventricular administration allows more uniform distribution throughout the neuraxis [90] and can reach a concentration 10 times higher than LP [80], which ensures more robust antitumor activity and improved survival [53].

The surgical complication rate of ventricular reservoirs is low [85, 91, 92], even in cases with dysmorphic ventricles or slit-like ventricles [93]. Furthermore, employment of a ventricular reservoir not only gives access to the CSF cavity to deliver drugs but allows facilitation of the collection of CSF to control elevation of the intracranial pressure, measure drug concentrations to titrate drug concentrations, evaluate tumor markers to assess efficacy, and provides invaluable data to predict the prognosis through the collected data. Sometimes, even a small amount of CSF withdrawal will allow symptom alleviation in selected patients. Lastly, and importantly, it is less burdensome for both the clinician and patient.

The EANO-ESMO guidelines recommend that intrathecal chemotherapy should be considered for most patients with type IA/C LM [57], and should be administered through a ventricular rather than lumbar route whenever feasible [18]. The NCCN guidelines recommend intrathecal chemotherapy for good risk patients [66].

5.1.2.1. Methotrexate Methotrexate is the most commonly used agent in LM, and regardless of body weight, surface area, the volume is 10–15 mg twice per week [80]. Methotrexate has a half-life of 4.5 h and declines to subtherapeutic levels within four days [94]. It has been reported that up to 61% show complete cytologic response, with few or no patients showing neurologic improvement or recovery of function [54, 95]. Oral leucovorin, which does not enter the CSF, is administered to counter systemic MTX toxicity. Other neurologic toxicities related to MTX include delayed leucoencephalopathy, aseptic meningitis, acute encephalopathy, and transverse myelopathy.

5.1.2.2. Cytarabine Cytarabine may be administered intrathecally in two forms: standard and liposomal (DepoCyt). Liposomal cytarabine is a sustained release formulation of cytarabine prescribed once every 2 weeks [55]. DEPOSEIN was the first randomized trial to show clinical benefit from intrathecal chemotherapy in LM from a designated type of solid cancer [58]. The report demonstrated clinically meaningful gain in LM-related PFS when breast cancer patients with newly diagnosed LM received intrathecal liposomal cytarabine chemotherapy together with systemic treatment compared with systemic treatment alone [58].

5.1.2.3. Trastuzumab Intrathecal administration of trastuzumab to HER2 positive LM patients has also been repeatedly reported. Trastuzumab prolongs OS in patients with HER2 positive breast cancer LM who continue systemic treatment. This is achieved due to the high efficacy of trastuzumab treating the extra CNS compartment [96, 97], but due its poor CNS penetrance, its action within the CNS remains limited. Even when the blood-brain barrier (BBB) is disrupted due to local disease or following CNS radiation, trastuzumab still does not reach therapeutic concentrations in the CSF [98]. A previous pharmacologic study found that trastuzumab concentration in the CSF was 300 times lower than its concentration in the serum after intravenous administration [99]. A metanalysis of 24 articles with meta-regression (containing data of 58 patients) indicated that the OS in patients with breast cancer LM treated with intrathecal trastuzumab was 13.2 months compared to a median survival of 1.75–4.5 months [39]. It is well tolerated, yet this strategy needs further prospective trials to better address the impact on overall survival and quality of life.

5.1.2.4. Other intrathecal approaches Recently, a case report described the use of Nivolumab for melanoma intrathecally without notable adverse effects, one patient with an impressive radiographic and clinical response to treatment [100]. It is of particular importance to study the safety and efficacy of intrathecal immunotherapy in other primary cancer types.

Translational research of intrathecal administration therapies is still in its infancy. The lack of platforms to obtain objective data has been an obstacle. Recently, several studies have successfully created mouse models to aid this issue [101–103]. Elucidation of a promising treatment that can be used clinically is no longer something that can come from fortuitous discoveries but derived from scientifically justified ideas.

5.2. Systemic chemotherapy

Theoretically, chemotherapeutics agents administered intravenously (IV) will distribute the same way as IV administrated contrast agents, and therefore can reach the systemic disease as well as the LM lesions. Increased CSF protein levels in LM patients indicate the disruption of the blood–CSF barrier and so there must be increased levels of systemically administered drugs in the CSF of most patients with LM. Retrospective studies reported nearly 20 years ago have suggested activity of systemic chemotherapy [82, 95, 104], but have not been updated, and therefore, it remains uncertain whether these agents improve the prognosis of LM. Furthermore, floating tumor cells in the CSF or diffuse leptomeningeal and ependymal spread of the disease are poorly covered by systemically administrated agents because drug distribution into the CSF depends mainly on drug transport across the choroid plexus and not the dysfunctional BBB [105].

Analogous to patients with brain metastasis, the best systemic treatment of LM is determined by the primary tumor and its molecular characteristics or the molecular characteristics of tumor cells in the CSF (when available) and prior treatment of the underlying malignancy [106].

5.2.1. Untargeted systemic chemotherapy

Even for patients with CSF flow abnormalities, systemic chemotherapeutic agents may allow uniform distribution, even with bulky tumors [95]. High-dose MTX is the most commonly used systemic agent in LM patients, but the clinical response remains inconclusive [82, 95, 107]. The need for close inpatient monitoring, including aggressive hydration and urinary alkalinization followed by leucovorin rescue is a time-consuming burden for this poor prognosis disease. Yet, it remains recommended for good risk patients in the NCCN guideline [66].

Several observational studies have reported the effect of capecitabine on patients with LM [104, 108]. A case series documented response to capecitabine and trastuzumab combination therapy in patients with breast cancer LM [109]. Compared to other regimens, capecitabine is unassociated with central neurotoxicity and is generally well tolerated [110]. However, practically, this is an option limited to the very few that have not been exposed to the drug yet. Temozolomide has been employed in a phase 2 study of LM from solid tumors with an observation of temporary disease stabilization in two patients [111], but remains uninvestigated thereafter.

5.2.1.1. Systemic therapy for breast cancer derived LM Currently, there is no consensus for choice of treatment specifically for these patients. Treatment options which generally rely on study results of patients harboring brain metastases consist of radiotherapy, systemic and/or intrathecal delivered chemotherapy, and improve the median overall survival to 3–8 months [26, 30, 57]. Unlike TKI treatment where CNS penetration may control NSCLC derived LM, there are no agents that show the same amount of penetration, although agents such as trastuzumab-emtansine, capecitabine are relatively active in the CNS, including tucatinib which is currently under investigation. In general, the current recommendation for breast cancer derived LM is high dose methotrexate (median survival is 5–6 months) or capecitabine which has induced responses and disease stabilization in some patients [112]. Again, this is unlikely to be a fair option for patients that have already succumbed to a certain degree of sickness.

A large real-life database of 22266 breast cancer derived LM patients identified a subgroup of patients with better prognosis which is the group where concomitant systemic therapy and IT methotrexate (rather than cytarabine or thiotepa) were used [37]. Data from many other retrospective studies also underpin the combination of intrathecal and systemic therapies with better outcomes [7, 30, 59].

5.2.2. Targeted systemic chemotherapy

5.2.2.1. Monoclonal antibodies Studies have shown high levels of VEGF in the CSF of LM patients which correlates with poor prognosis [113–115]. Combined therapy of bevacizumab, etoposide, and cisplatin (BEEP) therapy led to decreased leptomeningeal enhancement, negative CSF cytology, and overall survival of 8 and 7.5 months in two breast cancer patients [116]. A pilot study with a similar patient population reported median overall survival of 4.7 months and CNS response rate of 70% [117]. However, the combination of these cytotoxic agents might be burdensome for many LM patients.

5.2.2.2. Immune checkpoint inhibitors The benefit of immune check point inhibitors for LM is emerging but remains largely unknown. A recent phase 2 trial of Pembrolizumab in patients with solid tumor derived LM conferred a 38% CNS response rate in LM patients with tolerable safety, and deep responses in selected patients [118]. A retrospective study of patients with advanced NSCLC treated with ICIs showed that the six-month PFS rate was significantly higher in the NCCN LM good prognosis group (good versus poor prognosis group 40% vs 0%: $p = 0.05$) and can benefit from ICI treatment [119]. These responses might owe to the less effective blood-brain barrier in the presence of LM allowing the activated T cells to reach the CNS.

5.2.2.3. Small molecular inhibitors

• Epidermal growth factor receptor (EGFR) mutant NSCLC

A variety of EGFR mutations arise in 40–55% Asian patients, and 5–15% of Caucasians [120]. Tyrosine kinase inhibitors have CNS activity in these patients.

Osimertinib is a third-generation irreversible EGFR TKI that inhibits EGFR-sensitizing and T790M mutations with significant intracranial activity and was reported to achieved an 18.9-month duration of response, 11.0-month median overall survival with a manageable safety profile for patients with NSCLC that harbor T790M mutations [60]. This fits with the expectation that known targets and its companion agent will advance the treatment in LM. Afatinib is a second-generation drug also reported to have activity within the CNS even in osimertinib progressing, afatinib-naive patients [121]. The usage of erlotinib at a higher dose (e.g., 600 mg daily or 1500 mg once weekly) has been shown to have activity in LM patients in multiple studies previously, but is unlikely to be used in an upfront setting to treat LK in this 3rd generation TKI era, unless combined with bevacizumab.

• Anaplastic Lymphoma Kinase (ALK) rearrangement positive lung cancer.

ALK-rearrangement is seen in 3–5% of NSCLC, and up to 40% of patients have CNS spread at time of diagnosis. Crizotinib, a first generation ALK inhibitor does

not penetrate the BBB and displays modest, non-durable CNS activity even when effective against the systemic disease compared to later-generation drugs [122]. Lorlatinib is a third generation ALK inhibitor especially designed to penetrate the BBB [123] and displays high intracranial activity in treatment-naïve as well as pretreated ALK-positive NSCLC patients. Lorlatinib was active in two patients with LM in one report [124] and displayed a promising response rate of 77.8% in another [125].

6. Response assessment

The response assessment of LM requires three basic elements: a standardized neurological examination, cerebral spinal fluid (CSF) cytology or flow cytometry, and radiographic evaluation. In attempt to provide a framework for use in clinical trials, the Response Assessment in Neuro-Oncology (RANO) LM working group for assessing LM illustrated a series of standardize response definitions to allow cross-comparison of forthcoming LM trials [126].

6.1. Neurological assessment

The RANO LM working group in conjunction with the RANO Neurological Assessment working group created an instrument for assessing the neurological exam [127]. Progressive disease in LM based on neurological assessment is defined by a change of 2 or more levels in given domains (e.g., eye movements, facial strength, hearing etc.) or alternatively by a significant change of the severity of any symptom in one domain. As the majority of neurological deficits due to LM are irreversible, the best response to treatment is usually stabilization of neurological function. Not included in this score card but acknowledged are quality-of-life measures such as patient-reported outcomes (PROs) and other PRO measures such as pain or incontinence and these would add value in overall assessment by measuring the impact of the disease as well as treatment [128].

6.2. CSF assessment

CSF cytology is usually a qualitative measure and reported as negative, atypical, suspicious, or positive [12, 129, 130]. The definitive cytological diagnosis such as class 1 and 5 is straightforward, but the others are put under a perplex outcome measure in most cases, that is, to determine an atypical report as negative and likewise, a suspicious diagnosis as positive. Progressive disease is defined by either conversion of negative to positive CSF cytology or failure to convert positive cytology to negative following treatment induction.

The RANO LM working group recognizes the duration of response to be important and defines a positive cytological response as where the CSF is cleared of

identifiable tumor cells and maintains that status for 4 weeks. Nonetheless, the sensitivity of CSF cytology is poor and the potential of making a declaration of "response" even though tumor cells are still present in CSF but not found (i.e., a false negative) may be as high as 50% [129]. In the contrary, the interpretation of positive CSF cytology in an otherwise stable patient is also difficult. For these reasons, some recent RCT's do not include the conversion of cytology as a primary response criterion in solid-tumor derived LM.

CSF protein, glucose, and cell count is not recommended in assessing response, as these adjunctive measures rarely reflect treatment-response but might be useful in other clinical contexts such as treatment-related toxicity or CSF cytology–negative LM. The use of novel biomarkers such as tumor antigens, signaling pathway molecules involved in extravasation, adhesion, migration, angiogenesis, cell free DNA, and chemokines are currently being evaluated as to a role for improved detection, treatment and response assessment tool for LM, but yet to be validated [47, 113, 131–133].

6.3. Neuroimaging assessment

Another challenging aspect of response assessment in LM is the neuroimaging evaluation. Whether MRI assessment can replace CSF analysis has never been focused on, primarily as (i) there are no criteria for adjudicating response by MRI in LM disease, (ii) MRI is underused in a standardized manner in RCT of LM disease, and (iii) perhaps most importantly, normal MRI assessment in patients with LM disease is not infrequent. MRI assessment of the CNS disease is useful only when positive and as such in patients with negative MRI, alternative methods of response are required.

Nodules in the subarachnoid space or ventricles are often difficult to measure because they are small (often <5 mm), inter-connected by linear enhancement, and subject to inter-MRI variability due to slice positioning and contrast conspicuity. The RANO LM working group advises that nodular disease that is ≥5 × 10 mm in orthogonal diameters be defined as measurable disease and be serially assessed in follow-up imaging. Synchronous or metachronous presence of parenchymal brain or spine metastases should be considered separately from response definitions for LM and would be adjudicated disjointly as previously described [134]. A follow-up on the RANO recommendation indicated that the instructions on the scorecard where impractical, resulting in no acceptable alpha concordance coefficient was obtained for the rating of single items at baseline or follow-up [135]. Central imaging review of patients with LM has remains to be challenging, and likely will require future revisions as additional knowledge and use are gained.

7. Conclusion

LM remains as a devastating complication and carries a very poor prognosis, even when treated. During the past decades, the incidence of LM has increased, probably as a result of higher success rates of systemic treatments resulting in more patients achieving long-term survival, and subsequently, allowing LM to develop, and the versatility of higher resolution imaging modalities. The clinical outcome of LM has been improved in the era of advanced diagnostics and refined therapeutic strategies with immunotherapy and molecularly targeted therapy in selected tumors. Whereas optimal, as well as immediate symptomatic control is required in many cases, the awareness and prompt diagnosis of this rapid deteriorating complication remains to be an imperative step of the disease. Intrathecal injections have been historically a primary therapy to treat LM, however, frequently indicated as a treatment not established in randomized trials and tend to be withheld in recent studies. Apart from systemic treatment for target driven tumors, a provocative, but practical suggestion would be to place an Ommaya reservoir, withdraw CSF to achieve immediate symptom relief which will allow simultaneous CSF samples to evaluate, and initiate intrathecal injections and attempt to regain a better performance status to allow subsequent systemic therapy.

Data availability

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Conflicts of interest

The authors have stated that they have no conflicts of interest.

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