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# Leptomeningeal metastases from solid malignancy: a review

Sophie Taillibert[1], Florence Laigle-Donadey[1], Catherine Chodkiewicz[2], Marc Sanson[1], Khê Hoang-Xuan[1] and Jean-Yves Delattre[1]
[1]*Fédération de Neurologie, Groupe hospitalier Pitié-Salpétrière, Paris, France;* [2]*Department of Interdisciplinary Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida, USA*

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**Summary**

Leptomeningeal metastases (LMM) consist of diffuse involvement of the leptomeninges by infiltrating cancer cells. In solid tumors, the most frequent primary sites are lung and breast cancers, two tumors where the incidence of LMM is apparently increasing. Careful neurological examination is required to demonstrate multifocal involvement of the central nervous system (CNS), cranial nerves, and spinal roots, which constitute the clinical hallmark of the disease. Cerebro-spinal fluid (CSF) analysis is almost always abnormal but only a positive cytology or demonstration of intrathecal synthesis of tumor markers is diagnostic. T1-weighted gadolinium-enhanced sequence of the entire neuraxis (brain and spine) plays an important role in supporting the diagnosis, demonstrating the involved sites and guiding treatment. Radionuclide CSF flow studies detect CSF compartmentalization and are useful for treatment planning. Standard therapy relies mainly on focal irradiation and intrathecal or systemic chemotherapy. Studies using other therapeutic approaches such as new biological or cytotoxic compounds are ongoing. The overall prognosis remains grim and quality of life should remain the priority when deciding which treatment option to apply. However, a sub-group of patients, tentatively defined here, may benefit from an aggressive treatment.

## Introduction

Leptomeningeal metastases (LMM) result from diffuse infiltration of the leptomeninges by malignant cells originating from an extra-meningeal primary tumor site. Meningeal dissemination is an important issue in neuro-oncology because its incidence is increasing and because the clinical consequences are severe. Over the last decades, important advances have been made in earlier diagnosis of the disease but they have not been accompanied by substantial therapeutic progress. This review focuses on LMM originating from solid systemic tumors excluding leptomeningeal dissemination of hematological malignancies or primary brain tumors.

## Epidemiology

The incidence of LMM in patients with solid tumors ranges from 4 to 15% [1–8]. In the Memorial Sloan Kettering Cancer Center experience, an 8% incidence of LMM was reported in 2375 patients with cancer, on postmortem analysis.

Although any cancer can seed the leptomeninges, the main culprits are breast and lung cancers, head and neck cancers, melanoma and gastric cancer (Tables 1 and 2). In some tumors, particularly breast or small-cell lung cancer, the incidence of LMM is increasing and several hypotheses have been put forward to explain this finding. Firstly increased survival and better systemic control of the cancer allow the late expression of LMM. Secondly, the meninges are a sanctuary for many cytotoxic agents that have difficulty crossing the intact blood–CSF barrier. In this setting, subarachnoid tumor cells are not adequately treated and may proliferate, as previously observed in acute leukemias. Combination of these factors probably explains the considerable rise in actuarial incidence of LMM in SCLC over time, from 0.5% at diagnosis to 25% after 3 years of survival and the observation that isolated meningeal involvement is no longer an exceptional site of relapse after chemotherapy for breast cancers, particularly when taxanes or trastuzumab are used, both of which diffuse poorly in the CSF [15–18]. Thirdly, the increased rate of premortem diagnosis, relying on higher awareness and neuroimaging studies, especially Gd-enhanced MRI of the entire neuraxis, also improves identification of this disease [15]. Occasionally, LMM may even be detected on MRI when the patient is asymptomatic and the CSF analysis is not contributive. Nevertheless, the incidence of LMM remains higher in some post-mortem series compared to clinical ones (e.g. 25% vs. 11% in the National Cancer Institute study of small-cell lung cancer), possibly because LMM generally occurs late in the course of systemic cancer when non-specific neurological symptoms such as confusion do not necessarily lead to extensive investigations [15]. In addition, LMM are often associated with other central nervous system (CNS) metastases, particularly in the brain (33–75%) or dura (16–37%), which may dominate the clinical picture[1,5,16,19]. In about 20% of cases, meningeal involvement is the first metastatic site [1].

*Table 1.* Distribution of LMM by type of cancer [1–6]

| Type of cancer | % |
|---|---|
| Breast carcinoma | 12–34 |
| Lung carcinoma | 10–26 |
| Melanoma | 17–25 |
| Gastrointestinal tract cancer | 4–14 |
| ACUP (Adenocarcinoma of unknown Primary) | 1–7 |
| Others: | Not estimated |
| Prostate | |
| Head and neck | |
| Squamous cell carcinoma | |
| Thyroid cancer | |
| Rectal cancer | |
| Carcinoid tumor | |
| Rhabdomyosarcoma | |

*Table 2.* Frequency of leptomeningeal metastatic involvement by type of cancer

| Type of cancer | Frequency of secondary LMM (%) |
|---|---|
| Melanoma | 22–46 [9,10] |
| Small-cell lung cancer | 10–25 [11,12] |
| Breast carcinoma | 5 [13] |
| Head and neck tumors | 1 [14] |
| Non-small-cell lung cancer | 1 [14] |

## Pathogenesis and pathology

### *Pathogenesis*

Cancer cells may invade the meninges through different pathways, depending on histological type of the primary tumor [16,20,21]:

*Hematogenous spread*
Hematogenous spread to the arachnoids itself via the arterial circulation, is probably the commonest route of extension, but seems less common in solid that in hematological malignancies [20,21]. Also, seeding of the leptomeninges via retrograde venous pathways along the valveless Batson's venous plexus has been incriminated in prostate cancers but this hypothesis remains speculative [22,23].

*Spread via the endoneural/perineural and perivascular lymphatics route*
Vertebral and paravertebral metastases (particularly from breast and lung cancers) as well as head and neck cancers may spread along "peripheral or cranial nerve" [21] via the endoneural/perineural route or along the lymphatics or veins [20], then through the dural and arachnoidal sleeves of nerve roots (spinal roots, cranial nerves) into the subarachnoid space.

*Direct spread from the CNS*
Direct spread from metastases located in the CNS parenchyma and making contact with the meninges has been described. These tumors may breach into the subarachnoid or ventricular spaces and diffuse widely in the CSF, although a peritumoral fibrotic reaction often circumscribes this type of dissemination [24].

Choroid plexus metastases and subependymal metastases may also cause CSF dissemination [1].

*Iatrogenic spread*
During invasive procedures or neurosurgery, tumor spread to the leptomeninges through an ependymal or dural breach is a potential complication [25–27].

Once malignant cells enter the CSF, they disseminate by extension along the meningeal surface and by CSF flow to distant parts of the CNS where they settle and grow, forming secondary leptomeningeal deposits. While a diffuse covering of the leptomeninges is particularly frequent in hematological malignancies, plaque-like deposits with invasion of the Virchow–Robin spaces and nodular formations are more characteristics of solid tumors. The areas of predilection for circulating cell settlement are characterized by a slow CSF flow and a marked gravity, including basilar cisterns, posterior fossa and cauda equina [24].

Subsequently metastatic nodules may also invade subpial CNS parenchyma or peripheral nerves (spinal roots or cranial nerves).

### *Pathology*

*Macroscopy*
Gross inspection of brain, spinal cord and spinal roots may be normal. Most often the leptomeninges present abnormalities such as thickening and fibrosis that may be either diffuse or localized in one or several distinct area(s), particularly areas of relative CSF flow stasis, as stated above [28,29].

*Histological findings*
There is a diffuse or multifocal infiltration of arachnoid membranes by cancer cells, filling the subarachnoidal and Virchow–Robin spaces, sometimes invading the underlying neuraxis, vessels and nerve surfaces. Cranial and spinal nerve demyelination and axonal degeneration are sometime observed without any tumor infiltration. Microscopic examination may also reveal infarction of infiltrated areas [5,29,30]. A pure encephalitic variant is characterized by massive invasion of the Virchow–Robin spaces, without infiltration of the sub-arachnoidal spaces of the brain surface [31].

## Pathophysiology of signs and symptoms

Several mechanisms, often combined, are incriminated:

### *Hydrocephalus and increased intracranial pressure*

Tumor infiltration of the base of the brain, sylvian fissures, and arachnoid villi as well as reactive fibrosis and inflammatory response may block CSF outflow and lead to hydrocephalus and increased intracranial pressure. However, when the disease is located near the sagittal sinus, intracranial pressure may be elevated in the absence of overt hydrocephalus [32].

*Compression and invasion*

Focal neurological symptoms and signs, and increased intracranial pressure may result from compression or invasion of the brain and spinal cord, as well as cranial and peripheral nerve roots [16].

*Ischemia*

Invasion, compression or spasm of blood vessels that are located on the brain convexity or in the Virchow–Robin spaces interfere with the blood supply and oxygenation of neurons and may produce transient attacks, strokes, and probably also a more diffuse encephalopathy correlated to a decrease in cerebral blood flow [33].

*Metabolic competition*

Some patients develop a diffuse encephalopathy of unknown origin and it has been suggested that tumor cells and neurons could be in competition for metabolites such as glucose leading to relative deprivation of the underlying neurons [34].

*Blood–cerebrospinal fluid barrier disruption*

A disruption of the blood–CSF barrier is rarely the consequence of a direct invasion of the plexus choroids and is more commonly due to the development of a tumoral angiogenesis consisting of leaky fenestrated neovessels which develop as soon as the tumor reaches a threshold diameter (nodules) or thickness (layers) [29]. The blood–CSF barrier is abnormal at this level, as illustrated by contrast enhancement of the metastatic meninges on MR scans. Nevertheless, breakdown of the blood–CSF barrier in LMM is only partial since only a minority of patients responds well to systemic water-soluble chemotherapy, even when other extra-meningeal systemic metastases are sensitive to this regimen.

## Diagnosis

Early diagnosis of LMM is crucial because response to treatment and survival are correlated with performance status, neurological disability, and subarachnoid tumor burden.

*Clinical features*

Random and asymmetric distribution of symptoms and signs reflects the multifocal nature of the disease that may involve the entire neuraxis, in various combinations, brain, spinal cord, cranial nerves and spinal roots [1,4,5,9]. Signs suggestive of leptomeningeal irritation, such as nuchal rigidity or pain on straight leg rising occur in only 15% of patients. The key feature is therefore the discovery of multifocal signs, often without associated symptoms such as radicular pain and headaches (Tables 3–5), demonstrating a more widespread disease diffusion than previously suggested.

*Table 3.* Most frequent cerebral symptoms and signs in patients with LMM from solid tumors

| Symptom | Initially (%) | At any time (%) | Sign | Initially (%) | At any time (%) |
|---|---|---|---|---|---|
| Headache | 38 | 40 | Papilledema | 12 | 12 |
| Mental change | 25 | 30 | Abnormal mental state | 50 | 50 |
| Nausea and vomiting | 12 | 20 | Seizures | 14 | 15 |
| Gait difficulty | 46 | 68 | Extensor plantar(s) | 50 | 66 |

Data combined from Olson et al. [1], and Wasserstrom et al [5].
Total > 100% because many patients had more than one symptom or sign.

*Table 4.* Most frequent cranial nerve symptoms and signs in patients with LMM from solid tumors

| Symptom | Initially (%) | At any time (%) | SIGN | Initially (%) | At any time (%) |
|---|---|---|---|---|---|
| Visual loss | 8 | 12 | Ocular muscle paresis | 30 | 38 |
| Diplopia | 8 | 20 | Trigeminal neuropathy | 12 | 14 |
| Hearing loss | 6 | 9 | Facial weakness | 25 | 26 |
| Dysphagia | 2 | 4 | Hearing loss | 20 | 20 |

Data combined from Olson et al. [1], and Wasserstrom et al [5].

*Table 5.* Most frequent spinal symptoms and signs in patients with LMM from solid tumors

| Symptom | Initially (%) | At any time (%) | Sign | Initially (%) | At any time (%) |
|---|---|---|---|---|---|
| Pain | 25 | 40 | Nuchal rigidity | 16 | 17 |
| Back | 18 | 50 | Reflex absence/decrease | 60 | 76 |
| Radicular | 12 | 25 | Dermatomal sensory loss | 50 | 50 |
| Paresthesias | 10 | 42 | Lower motor neuron weakness | 78 | 78 |
| Weakness | 22 | 50 | | | |

Data combined from Olson et al. [1], and Wasserstrom et al [5].

Brain involvement often causes mental change, headaches, seizures, and gait disturbance [28]. Clinical presentation may be confusing when it simulates psychiatric disorder or is related to a metabolic disorder such as diabetes insipidus (breast carcinoma) [5,16,35,36]. Uncommon clinical findings include central hypoventilation [37] and pure encephalitic form, which is characterized by confusion, seizures, and focal neurological signs contrasting with normal MRI [31,38].

The most frequently affected cranial nerves are the oculomotor nerves followed by the facial, optic, and auditory nerves. Spinal root involvement produces back and radicular pain, which are often associated with lower motor neuron weakness and dermatomal sensory loss. Loss of one or several deep tendon reflexes is found at diagnosis in up to 70% of patients and constitutes an excellent sign to demonstrate multifocal involvement.

*CSF examination*

The most informative diagnostic procedure in LMM assessment is lumbar puncture. CSF is usually abnormal regardless of the results of CSF cytology. Fewer than 5% of patients present a normal opening pressure, cell count, protein and glucose rates and a negative CSF cytology [5,39]

Specific and non-specific tests are reported in Table 6, and commented below. As a consequence of CSF flow obstruction, CSF pressure is elevated in at least 50% of patients [16]. CSF protein concentration is elevated in about 80% of cases. In the absence of infection, hypoglycorrhachia (absolute level of less than 40 mg/dl) is highly suggestive of LMM and is present in 25–40% of cases [16]. It is important to note that abnormal protein or glucose levels are sometimes found only in the lumbar space while the ventricular levels remain normal.

The discovery of malignant cells in the CSF is the key diagnostic feature. Unfortunately, the initial cytology is (falsely) negative in up to 40–50% of patients with pathologically proven LMM [19]. Repeated sampling enhances the diagnostic yield (from 50 to 90% between first and third spinal tap) justifying the recommendation to perform at least three lumbar punctures over several days if the initial cytology is negative [5,19]. Diagnostic yield also improves with CSF sample volume (10 cc at least) and with immediate processing of the samples in the laboratory. The sampling site is also important for cytological examination with frequent ''positive'' lumbar CSF accompanied by '' negative'' ventricular fluid, while the opposite is rare [40,41]. The yield of cytological assessment increases when meningeal involvement is diffuse or when the sampling site is closer to the main focus of disease [19].

Because the sensitivity of cytology analysis is imperfect, considerable efforts have been made to develop additional laboratory tests (Table 6). Overall, these tests can be very useful in some tumor types but they have often been disappointing in terms of specificity or sensitivity, and several of them have not reached wide clinical use.

Non-specific markers such as $\beta$-glucuronidase or lactic acid dehydrogenase (LDH) isoenzymes may be suggestive of LMM (for example, a $LDH_5$ greater than 10% of the total LDH in CSF) but they do not permit a formal diagnosis, even after careful attempts to exclude infection or other non-neoplastic causes of CSF inflammation [52, 53]. In fact, non-specific tests are mainly useful for therapeutic follow-up. Caution must be observed when ventricular CSF is examined because of the discrepancies between the composition of ventricular and lumbar CSF, including cytology and CSF markers.

*Neuroimaging*

*Brain and spinal MR*

MR of the brain *and* spine with a T1-weighted gadolinium-enhanced sequence is the standard and most

*Table 6*. CSF laboratory exams with some specificity during LMM

| | |
|---|---|
| *Routine* | |
| Cytologic examination | Positive |
| *Biochemical markers [42, 43]* | |
| CEA | >1% of serum rate |
| AFP | >1% of serum rate |
| $\beta$ HCG | >1% of serum rate |
| melanin | Presence in the CSF |
| CA 125 | >1% of serum rate |
| CA15-3 | >1% of serum rate |
| 5 HIAA | High elevation / usual CSF rate |
| PSA | >1% of serum rate |
| *Biomolecular techniques* | |
| Flow cytometry [44–46] | Aneuploid cells<br>Hyperdiploid cells +++<br>Presence of CEA on cells surface |
| DNA single cell cytometry [47] | |
| FISH (interphase cytogenetics) [48] | Numerical or structural aberrations in interphase nucleus |
| RT-PCR markers [49]: | |
| MAGE, MART-1, tyrosinase | Positive in melanoma cells of the CSF |
| *Immunocytochemical analysis [50,51]* | |
| protéine S-100 | Positive in melanoma cells of the CSF |
| HMB45 | Positive in melanoma cells of the CSF |
| TTF 1 | If primary cancer unknown: orientates towards lung and thyroid carcinoma |

sensitive radiological technique when LMM is suspected [54, 55]. The superiority of MRI over CT is well established with 1.5–2 times higher specificity and sensitivity [56–70]. It is important to perform MRI before CSF examination because a spinal tap alone can probably be followed by long lasting (weeks to months) diffuse meningeal enhancement. The rate of false negative MRI is about 30% and could be further diminished by the use of a higher amount of gadolinium [71]. In solid tumors, the yield of contrast-enhanced MRI to detect LMM is higher that in hematological malignancies because bulky disease is more frequent [72].

The characteristic aspects of LMM on MRI are indicated on Table 7. Particularly suggestive are contrast-enhancement of the meninges (Figure 1) and sulci, ventricular ependyma, basilar cisterns, tentorium, cauda equina (Figure 2) and hydrocephalus. Although MRI is not specific, it may be sufficient to establish the diagnosis, even if CSF cytology is negative, when it shows multifocal contrast enhancing subarachnoid nodules in a patient whose primary cancer is identified, known for its propensity to seed the meninges, and often disseminated or associated with other CNS metastases [72,75]. When the primary cancer is unknown and when CSF cytology is negative, MRI alone is not sufficient to establish the diagnosis that requires histological confirmation. The differential diagnosis including infectious and inflammatory causes of subacute/chronic meningitis may provide similar images to LMM on MRI [76]. In patients without malignant cells in the CSF, careful confrontation between oncological data, neurological findings, MRI and other laboratory tests are therefore needed to make a reliable diagnosis of LMM [73,74].

*CSF flow studies*

Today two methods using either radionuclides (indium 111-DTPA [diethylene triamine pentaacetic acid]) or MR are performed for the assessment of CSF circulation and its potential compartmentalization [9,56,70,77–82]. Formal comparison has not been made between these procedures. Flow blocks are observed in at least 30–40% of patients with LMM and are predominantly located at skull-base or next to filum terminale.

*Table 7.* MR scans findings with LMM [73,74]

| |
|---|
| Intradural enhancing nodules in spinal canal (Figure 2) |
| Enhancement and enlargement of cranial nerves |
| Superficial linear sulcal, cisternal or dural enhancement |
| Irregular tentorial enhancement |
| Irregular ependymal enhancement |
| Cisternal or sulcal obliteration |
| Hydrocephalus |
| Subarachnoid-enhancing nodules (Figure 1) |
| Intraventricular-enhancing nodules |
| Multiple small nodular superficial brain nodules |
| Spinal linear enhancement (Figure 1) |
| Spinal cord enlargement |
| Asymmetry of the roots |

*Other imaging studies*

Anecdotal cases of LMM detected by 18-FDG PET and 11C-Methionine PET scans have been reported in lung and breast cancer patients. Cerebral angiography is very rarely indicated when patients with LMM present acute symptoms suggesting a stroke [5,30,83]. Irregular narrowing of arteries at the base of the brain, due to either spasms of pial vessels or tumoral infiltration of their walls may sometimes be observed, but these images are not specific.

*Meningeal biopsy*

A meningeal biopsy is considered when the diagnosis remains uncertain and other causes of chronic meningitis have been excluded (see below) [84]. The biopsy should target a symptomatic and/or contrast enhancing area on MRI. Cisterns at the base of the brain and leptomeninges of the cauda equina are often chosen for this procedure [16].

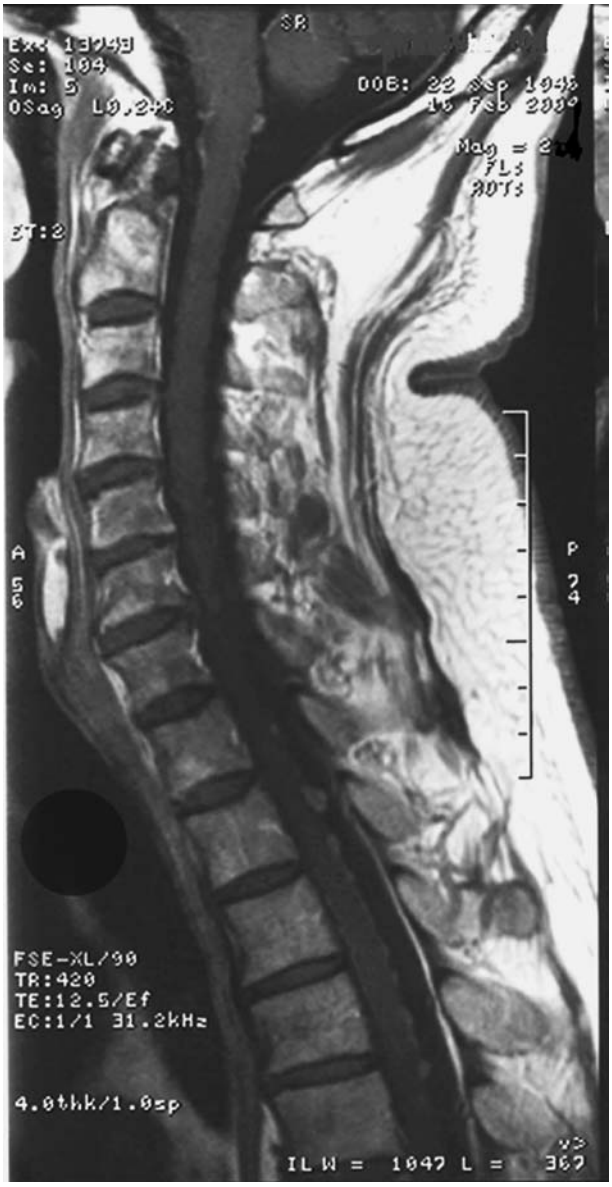


*Figure 1.* Sagittal T1-weighted MR with Gadolinium showing a spinal linear and nodular enhancement.

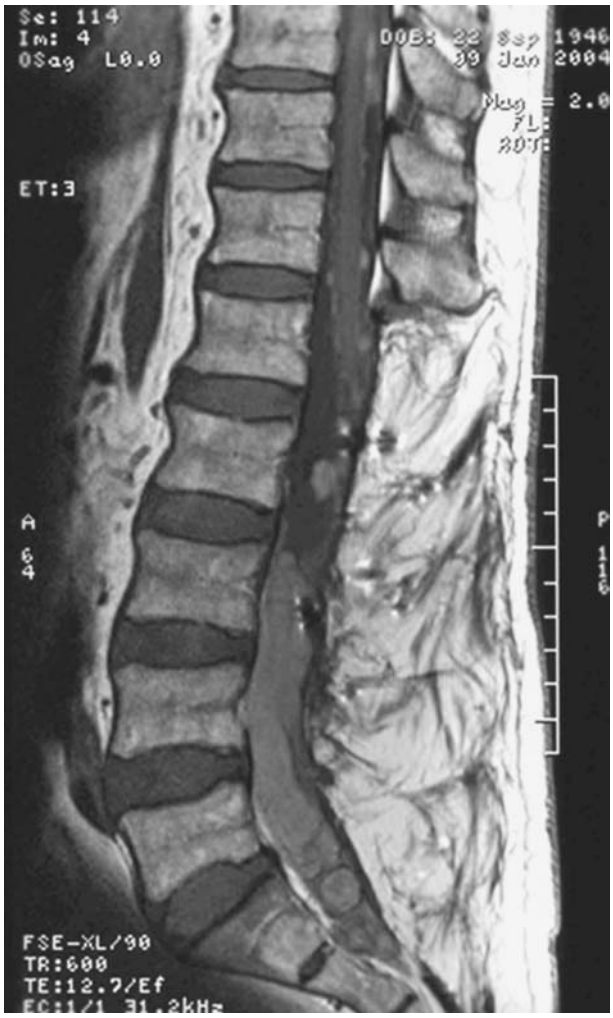


*Figure 2.* Sagittal T1-weighted MR with Gadolinium showing "bulky" contrast enhancing nodules in the cauda equina area.

*Differential diagnosis*

In patients with a known progressive primary cancer, the diagnosis of LMM is usually easy. Difficulties occur when CSF cytology is negative and when the primary tumor is not known or if its responsibility can be questioned (for example the primary tumor appears to be completely cured and has no propensity to metastasize to leptomeninges). In these cases, other etiologies of subacute and chronic meningitis must be ruled out [85]. Typically, patients with infections have more meningeal symptoms and signs than fixed neurological findings while the situation is reversed in LMM. Finally, when a meningeal tumor reveals the disease but the systemic work up cannot identify a systemic tumor, a primary meningeal glioma, PNET or PCNSL should be excluded as well as other rare causes of meningeal tumors such as isolated primary meningeal melanomas or rhabdomyosarcomas of the leptomeninges [33,86–89].

## Treatment options

In LMM from solid tumors, the therapeutic goals remain palliative, combining symptomatic and specific treatments.

*Symptomatic treatment*

Pain relief is required for headaches, back and radicular pain, using analgesics of increasing efficacy from paracetamol to opioids. In addition neuropathic pain often requires amitriptyline, clonazepam or antiepileptic drugs (such as gabapentin, carbamazepine and lamotrigine). Focal irradiation of symptomatic sites is often quite efficient in relieving pain. Seizures are managed with AEDs, but prophylactic administration of AEDs is not recommended in patients who have never had seizures.

Headaches related to edema or increased intracranial pressure can sometimes be handled with steroids, even if the contribution of steroids in LMM is modest as compared to brain metastases. In cases of hydrocephalus secondary to CSF blockade, a course of steroids during whole brain or skull-base radiotherapy is sometimes appropriate but shunting is often required in this situation. Repeated lumbar punctures in the absence of threatening associated brain metastases are often a good way to relieve headache.

*Surgery*

The main surgical treatments of LMM are ventriculoperitoneal shunting for hydrocephalus and placement of an intraventricular (rarely lumbar) Ommaya reservoir implanted subcutaneously in the scalp and connected to the ventricle via an outlet catheter for intrathecal chemotherapy. When both shunts are needed, an on-off valve may be placed but this implies that the patient can tolerate having the shunt turned off for a few hours after drug administration [73].

Complications of ventriculoperitoneal shunting include peritoneal dissemination of the tumor and infection but the main risk is poor efficacy because the shunts often dysfunction and clog in LMM, requiring repeated replacements.

When an Ommaya reservoir is placed, it is important to check the correct placement of the catheter by CT-scan before drug administration [90–92]. Hemorrhage at the time of placement occurs in less than 1% of patients but infection mainly due to *Staphylococcus epidermidis* complicates about 5–10% of the procedures [91–93]. The intraventricular device can sometimes be kept in place when antibiotics administered by intravenous and intraventricular routes are rapidly successful [93–96]. But, in our experience, removal is often necessary, possibly followed by replacement of the reservoir [97]. An unusual complication in patients with increased intracranial pressure, is CSF track along the catheter, resulting in subgaleal collections of CSF, which may become infected and require revision or replacement with a ventriculoperitoneal shunt [29].

*Radiotherapy*

Irradiation of the entire neuraxis is too toxic in these patients who have generally already received multi-agent chemotherapies and are prone to severe bone marrow toxicity. Focal radiotherapy (RT) of symptomatic areas

and of bulky disease observed on MRI is therefore the standard procedure, combined with chemotherapy. Irradiation ensures that tumors located in areas which are not reached by intrathecal chemotherapy (e.g., deep inside of bulky regions) also receive adequate therapy [98]. RT is generally administered at a dose of 30 Gy delivered in 10 fractions over 2 weeks. It provides effective relief of pain and stabilizes neurological symptoms but rarely leads to significant recovery (demyelination and axonal injury may persist in the absence of infiltrating cancer cells), hence the need for early treatment [99]. Thus, even in the absence of macroscopic disease on MRI, lumbar-sacral irradiation is indicated in case of symptomatic involvement of the cauda equina (low back pain, legs weakness, sphincter dysfunction) and skull-base RT is used in patients with cranial neuropathies [16]. Radiotherapy is also indicated to relieve CSF blocks which reduce the efficacy and increase the toxicity of intrathecal chemotherapy [1–7]. According to Posner and coll., whole brain radiotherapy should be delayed until hydrocephalus or focal seizures appear.

Other types of RT consist of intra-CSF administration of radioactive nuclides [100–102] or radiolabeled monoclonal antibodies but these procedures remain experimental [103–105].

### *Chemotherapy*

Chemotherapy is the only modality allowing simultaneous treatment of the entire neuraxis [106–108]. It can be administered intrathecally and/or systemically.

#### *Intrathecal chemotherapy*

The normal blood–brain and blood–CSF barriers limit the penetration into the CNS of most systemically administered anticancer agents. Consequently, CSF exposure to most cytotoxic agents is less than 10% of the plasma concentration. In LMM, the blood–CSF barrier is compromised but its breakdown is not complete and varies from one region to the other.

The goal of intrathecal chemotherapy is therefore to bypass the blood–CSF barrier, maximizing drug exposure in the CSF while reducing systemic toxicity. With this approach, a higher drug concentration can be achieved using a smaller dose, because the distribution volume of CSF is lower than that of the plasma (140 vs. 3500 ml) [109]. Furthermore, the half-life of most cytotoxic agents is longer in the CSF than in plasma, leading to prolonged CSF drug exposure that is particularly useful for cell-cycle specific agents such as methotrexate and cytarabine. Many areas of LMM are a few cells thick and the diffusion capacity of the drug (1–2 mm) is therefore appropriate for treating the tumor and even the most superficial part of the CNS parenchyma [103,110].

Intrathecal treatment can be delivered by repeated spinal punctures. Position affects ventricular drug levels after intralumbar administration and patients should remain flat for at least 1 h following treatment [111].

Intrathecal administration of the drug in the right lateral ventricle via an Ommaya reservoir is preferred because this procedure is painless and has several pharmacokinetic advantages over repeated LP including a better drug distribution in the entire subarachnoid ventricular spaces [112–114] and the possibility of delivering frequent small doses of drug to reduce "high concentration peak" and therefore the total cumulative drug dose as well as neurotoxicity .

Furthermore, injection in an Ommaya reservoir provides a certainty that the drug has not been given in the epidural space and can be used when the platelet count is $\geq 20{,}000$ cell/mm$^3$ while severe thrombocytopenia causes a significant risk of epidural or subdural hematoma after lumbar puncture.

Another method of intrathecal drug delivery which is seldom used is a lumbar catheter that is connected to a subcutaneously implanted reservoir.

#### *Drugs available for intrathecal treatment*

Methotrexate is usually the first line agent followed by cytarabine and thiotepa. Unfortunately, these drugs are not effective against some of the most frequent solid cancers associated with LMM, particularly melanoma and lung cancer.

##### *Methotrexate*

Therapeutic CSF concentrations, at 1 μM or more during 48–72 h, are obtained with a 12 mg dose in adults and children older than 2 [3,112,105–107]. Usually, the drug is initially administered on a twice-weekly schedule for 3–4 weeks, followed by a decrease in frequency over a total treatment time of 3–6 months. The exact duration of treatment has not been established, but some patients may benefit from prolonged treatment. Alternative schedules have been proposed such as the administration of intraventricular Methotrexate at 2 mg for 5 consecutive days every 2 weeks [106, 118,119]. Methotrexate is eliminated from the CSF to systemic circulation by CSF resorption. For that reason, predisposing factors that interfere with CSF resorption and increase toxicity should be searched for.

Folinic acid should be given orally or IV, 10 mg every six hours during 48 h, 24 h after methotrexate administration, in order to reduce systemic myelosuppression and mucositis. Leucovorin does not cross the blood–brain barrier in sufficient amounts to interfere with the central effects of methotrexate or its efficacy.

An accidental overdose of intrathecal methotrexate may result in significant morbidity or death. Standard recommendations include immediate drainage of CSF via lumbar puncture, ventriculostomy with ventriculolumbar perfusion, systemic steroids and systemic leucovorin administration. A potentially useful antidote, the Carboxypeptidase-G2 (CPDG2) has been reported. Pharmacokinetic studies showed a 400-fold decrease in CSF methotrexate concentrations within 5 min of CPDG2 administration [120].

##### *Cytosine arabinoside (Cytarabine, Ara-C)*

This drug is initially delivered at a dosage of 50 mg twice weekly and tapered in a similar way to that of

methotrexate. The half-life of Ara-C is much longer in the CSF that in serum because of the low levels of intra-CSF cytidine deaminase. The rapid deamination observed in the systemic circulation causes minimal systemic toxicities. A 'Concentration × Time' schedule has also been reported [121].

*DepoCyt®*

DepoCyt® is a liposome-encapsulated cytarabine formulation, which can be administered intrathecally once every 2 weeks. To date, it is approved by FDA only for leptomeningeal lymphoma. In solid tumors, a randomized trial comparing IT DepoCyt® to IT methotrexate found that Depocyt® increased time to neurologic progression (58 days vs. 30 days, $P = 0.007$) but did not affect survival. The number of patients' visits to the hospital was reduced by 75% in the DepoCyt® arm [122]. An additional phase III study is ongoing in solid tumor-LMM comparing DepoCyt® to methotrexate. In previous studies, the main side effect of DepoCyt® was arachnoiditis whose incidence was reduced by concomitant administration of oral dexamethasone (4 mg BID × 5 days). Pathologists should be informed of the administration of DepoCyt® because drug particles may be confused with erythrocytes.

*Thiotepa*

Thiotepa, an alkylating agent, is a second-line agent for breast cancer patients who do not respond to or cannot tolerate IT methotrexate. Occasionally, Thiotepa is delivered by the intrathecal route (10 mg twice a week), but there is no real pharmacological advantage to support this modality as compared to systemic administration. The efficacy and toxicity of intrathecal Thiotepa has been prospectively compared to intrathecal methotrexate in a randomized trial without statistically significant differences, although patients on the Thiotepa arm experienced fewer neurological toxicities [123].

*Systemic chemotherapy*

In contrast with lymphoproliferative neoplasms the benefit of intra-CSF chemotherapy in LMM from solid tumors remains modest. These disappointing results are due to several factors, including intrinsic chemoresistance, limited choice of drugs and the poor accessibility of bulky nodules to local treatment [124].

Furthermore, most patients suffering from LMM have active systemic disease which is a main cause of death [125]. Assuming that only patients with controlled systemic disease have prolonged off-therapy response of LMM [125–128], it is logical to use systemic chemotherapy in order to treat simultaneously systemic disease and LMM. Some authors consider that systemic therapy may even obviate the need for intrathecal therapy [125,126,128–130].

Siegal and coll reviewed intrathecal vs. systemic chemotherapy in LMM from solid tumors [125–131]. They concluded that adding intraventricular chemotherapy to combined radiotherapy and systemic chemotherapy in LMM from solid tumors (mainly breast cancers) did not change the overall response rate to treatment, either the median survival or the long-term survival rate, but significantly increased the rate of acute, sub-acute and delayed neurotoxicity. Conversely, systemic treatment is not always useful since another prospective study in LMM from non-small-cell lung cancer patients found that adding systemic chemotherapy to combined radiotherapy and intraventricular chemotherapy did not improve survival, a possible consequence of the low chemosensitivity of that type of cancer [132]. The choice of the most appropriate drug should be based not only on the chemosensitivity profile of the primary tumor and secondary (acquired) resistance but also upon the ability of this drug to reach efficient concentration in the CSF because of its chemical properties (lipophilic, low protein-binding, low molecular weight agents) or the possibility of administering high doses without unacceptable toxicity.

For example, it is possible to reach therapeutic intra-CSF levels with high dose IV methotrexate (higher than 3 g/m$^2$) or cytarabine (e.g. 3 g/m$^2$ every 12 h) [133,134]. Myelosuppression is the dose limiting factor of these treatment schedules [135].

Unfortunately, the use of these agents through a systemic route remains limited by their narrow spectrum of activity in most solid tumors. Hormonal agents such as tamoxifen, letrozole, anastrozole and megestrol have occasionally been useful in breast cancer-LMM [136,137].

*New therapeutic approaches*

*Chemotherapy*

*Systemic chemotherapy*. The challenge is to find new agents with proven efficacy in solid tumors which can reach adequate concentration in the CSF. Temozolomide, an alkylating agent that produces therapeutic CSF concentration when administered *per os* at conventional dosage, could be a candidate since it exhibits a wide range of activity against solid human tumors, including melanomas [138]. High-dose etoposide has been administered (1 g/m$^2$ for 3 days, every 4 weeks) in LMM from small-cell lung carcinoma with three complete responses in five treated patients [139]. This interesting preliminary result deserves further studies.

*Intrathecal chemotherapy*. Many efforts have been made to test new intrathecal treatments such as Diaziquone (AZQ) [140], mafosfamide [141], nimustine hydrochloride (ACNU) [142], 4-hydroperoxycyclophosphamide (4-HC), 6-Mercaptopurine(6-MP) [120,143–146], and Gemcitabine [147]. Unfortunately, none of these agents has shown clear evidence of activity.

In addition to Depocyt®, intrathecal administration of Methotrexate encapsulated in liposomes is being developed, but careful evaluation of its potential toxicity will be needed. Intrathecal instillation of a microcrystalline preparation of Busulfan (Spartaject) is also being studied in clinical trials against a large panel of tumors after having demonstrated its activity against chronic myelogenous leukaemia [148]. A microcrystalline formulation of temozolomide has also been developed and tested for intrathecal use in preclinical models of LMM.

Topotecan is a topoisomerase I inhibitor that shows anti-tumor activity against a wide variety of adult and childhood solid tumors. Experimental studies have shown that intraventricular administration of 1/100th of the systemic dose of topotecan could provide a 450-fold greater CSF exposure. A phase I study of intrathecal topotecan in patients with LMM has shown a response in 3 out of 13 patients suffering from LMM of primary brain tumors. Arachnoiditis was the dose-limiting toxicity. The efficacy of Topotecan in LMM originating from systemic solid cancer is currently unknown [149].

*Biological response modifiers*

New approaches such as viral-mediated gene therapy [150–152], signal transduction inhibitors [153–157], agents targeting angiogenesis (angiostatin) [157] or vascular cell adhesion molecules [158] are currently under investigation.

A major difficulty with biological response modifiers remains the poor CSF penetration after systemic administration as illustrated for Trastuzumab [159] (humanized monoclonal antibody targeting c-erb B2) and for SU5416 (inhibitor of the tyrosine kinase activity of the VEGF receptor) [160,161]. Attempts are therefore being made to develop these therapies for intrathecal use.

Clinical trials using $^{131}$I coupled to monoclonal antibodies against tumor antigenes directly injected into the CSF have been performed in solid tumors including melanoma, ovarian and breast primaries with rare occasional long-term clinical responses (7–26 months) [104,162–166]. The limits of this approach include the difficulty in creating specific monoclonal antibodies towards individual tumors, a limited effect on tumor cells at some distance from the bound cell, and the systemic toxicity of the released radiolabeled compound. Intra-CSF immunotoxins, coupling monoclonal antibodies or biological ligands, such as epidermal growth factor and transferred to a protein toxin have been studied in preclinical models [138,166–169] and in a pilot study including eight patients. A greater than 50% reduction of tumor cell counts in the lumbar CSF was observed in four patients, but seven of eight progressed. Side effects were transient and manageable with steroids and CSF drainage [170].

## Toxicity and complications of treatments

Most series describe a global complication rate of 70% with severe complications in 15–20% of cases, and treatment-related deaths in about 5% of patients [94,122,129,171]. Neurological complications are classified according to their time of occurrence (acute, subacute and delayed) and to the type of treatment (intrathecal or systemic chemotherapy) as illustrated in Table 8.

## Prognosis

A combination of focal radiotherapy and chemotherapy (intrathecal or systemic) constitutes the standard treatment of LMM although no prospective randomized trial comparing radiotherapy plus chemotherapy (intrathecal or systemic) to single modality treatment has been reported [4,172,173]. The type of the primary cancer is a major prognostic factor. For example, in a series of 90 LMM patients who received focal irradiation and intraventricular Methotrexate, 61% of breast cancer patients showed a neurological improvement or stabilization within a range of 2–20 months. Median survival in this group was 7.2 months and 15% of patients were alive at 1 year. In contrast, only 39 and 18% of the "lung carcinoma and melanoma group" respectively improved or remained stable within a range of 1–12 months with a median survival of 3–4 months and a 0% survival rate at 1 year [5].

Other studies have reported similar results with comparable treatment schedules [125,173–178]. According to these reports, it appears also that median survival of LMM from breast cancer can reach at least 6 months, which is superior to the observed survival in untreated patients which is approximately 10 weeks. Nevertheless, other series did not replicate such optimistic median survival [125].

Apart from tumor type, performance and neurological status, the bulk of CSF disease as well as the extent of systemic cancer also influence outcome in patients with LMM [131]. Fixed neurological deficits such as cranial nerves palsies, radicular weakness or paraplegia usually do not improve with treatment while encephalopathies may improve, particularly if the underlying causes such as hydrocephalus or seizures can be successfully treated by symptomatic measures. A bulky metastatic status of the CNS (parenchymal metastases, bulky leptomeningeal disease) and persistent blockade of the CSF flow after radiotherapy predict poor survival [72,125,179–181]. Impaired CSF flow dynamics is a poor prognostic factor, not only because it leads to inadequate drug distribution but probably also because it reflects meningeal tumor burden and correlates with extensive disease and worse prognosis. Finally, as previously stated, the status of systemic disease in patients with LMM is a predictive factor of clinical response of LMM.

## Guidelines

At the end of this review, tentative guidelines can be proposed. Several factors should be considered in decision-making including performance status, neurological findings (clinical, MRI, CSF flow dynamic) and evaluation of the primary tumor (nature and systemic dissemination).

Not all patients necessarily warrant aggressive treatment. Based on the analysis of prognostic factors, many patients are poor candidates for heavy therapy. Severe fixed neurological deficits rarely improve and therapy can result in significant neurological toxicities. These patients deserve optimal supportive care management with anti-emetics, narcotics and radiotherapy for symptomatic disease. Intraventricular chemotherapy should be avoided and may possibly be replaced by systemic chemotherapy in patients with bulky sub-

*Table 8.* Neurologic toxicities and complications of treatments for LMM [94,122,129,171]

| Nature | Timing | Agents | Clinical and radiological findings | Pathological findings | Treatment and course |
|---|---|---|---|---|---|
| Aseptic meningitis | Several hours after injection | Any IT agent | Mimics bacterial meningitis<br><br>CSF: pleocytosis, ↑ protein | | Oral anti-pyretics, anti-emetics and steroids<br>Reversible within 1–3 days<br>Further treatment possible |
| Acute encephalopathy | Within 24–48 h after treatment | IT MTX or Ara C, IV HD MTX | Seizures, confusion, disorientation and lethargy | | Usually totally reversible |
| Myelopathy | Within 48 h to months | IT MTX, Ara-C, Thiotepa | Myelopathy<br>CSF: ↑ protein<br>MR: spinal cord swelling, ↑signal on $T_2$WI, | Demyelination | Poor prognosis with persistent paraparesis (60%) |
| Subacute encephalopathy | 5–6 days after treatment | HD IV MTX | Stroke-like syndrome<br><br>CSF and MR: normal | | Reversible within 48–72 h<br><br>Further treatment possible |
| Acute cerebellar syndrome<br><br>Other: seizures, encephalopathy, myelopathy, | 2–5 days after treatment | HD IV Ara C ($> 3$ g/m$^2$) | Encephalopathy immediately followed by cerebellar syndrome<br>MR: cerebellar atrophy, reversible and diffuse leukoencephalopathy | Diffuse loss of Purkinje cells +/− WM demyelination | Recovery after treatment discontinuation<br><br>But may be permanent |
| Delayed leucoencephalopathy | Months to years after treatment | Typically combined RT + IV/IT CT | Subcortical-frontal syndrome<br>CSF: ↑ protein<br>MR: cerebral atrophy, diffuse WM ↑signal on FLAIR and $T_2$WI, ventricular dilatation | Disseminated foci of demyelination, axonal loss | |

*Abbreviations:* CSF: cerebrospinal fluid; CT: chemotherapy; ↑: elevated; H: hours; HD: high doses; IT: intrathecal; IV: intravenous; MR: magnetic resonance; MTX: Methotrexate; RT: radiotherapy; $T_2$WI: $T_2$ weighted-images; WM: white matter.

arachnoid nodules or concomitant parenchymal brain metastases.

In the absence of severe fixed deficits, breast cancer patients should be vigorously treated with radiotherapy, intrathecal and systemic chemotherapy because of their well-known potential for possible prolonged response to treatment. The indication of such a heavy treatment is more controversial for melanoma, non-small-cell lung cancers and other adenocarcinomas affecting the leptomeninges [137,182].

Because most LMM patients who respond to treatment die of systemic disease, the combination of radiotherapy, intrathecal chemotherapy, systemic chemotherapy (including new agents) and their optimal schedule should be prospectively re-evaluated in clinical trials. Overall, a too often nihilistic approach should be avoided in LMM favoring a more dynamic strategy mainly based on clinical research and trials.

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*Address for offprints*: Pr Jean-Yves Delattre, Fédération de Neurologie, Batîment Mazarin, Groupe hospitalier Pitié-Salpétrière, 47-83 bd de l'Hôpital, 75013 Paris, France; Tel.: +33-1-4216-0385; Fax: +33-1-4216-0418; E-mail: jean-yves.delattre@psl.ap-hop-paris.fr