Leptomeningeal carcinomatosis from solid tumours: a systematic review of the literature

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SUMMARY

Leptomeningeal carcinomatosis (LC), or neoplastic meningitis, is a disastrous complication of advanced cancer. This disease occurs in approximately 5% of patients with solid tumour and results from the dissemination of tumour cells from the cerebral spinal fluid (CSF) flow throughout the entire central nervous system (CNS). LC is characterized by multiple and fluctuant neurologic symptoms and signs. Useful tests for the diagnosis include magnetic resonance imaging (MRI) and CSF analysis. Unfortunately, the diagnosis remains challenging due to pleomorphic symptoms and false negative results of diagnostic procedures. For most patients, the aim of the treatment is to control symptoms, by using targeted radiotherapy and corticosteroids. More aggressive therapeutic approaches, such as intrathecal (IT) or systemic chemotherapy, should be restricted to highly selected and good-risk patients. Moreover, only few randomized clinical trials are available in the field and studies using more recent targeted therapies or immunotherapy should always be considered in these patients, as outcome with standard of care is disappointing.

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INTRODUCTION

Leptomeningeal carcinomatosis (LC) (also known as carcinomatous meningitis, or neoplastic meningitis) is a devastating complication of cancer because of its extremely poor prognosis. Fortunately, only 5% of advanced solid cancer patients are diagnosed with LC. However, an autopsy study has revealed that up to 19% of cancer patients with neurologic symptoms and/or signs have evidence of meningeal involvement. Furthermore, co-existing brain metastases (BM) are found in 50-80% of patients with LC, further increasing the neurologic morbidity observed in these patients.[1-3]

In cancer patients, the incidence of LC varies with the type of primary cancer and with the stage of the disease. The most common solid tumours giving rise to LC are breast cancers (12-35%, especially lobular carcinomas and HER2-positive diseases), lung cancers (10-26%, especially *EGFR* mutated and *ALK* amplified tumours), melanomas (5-25%), gastro-intestinal malignancies (4-14%) and cancers of unknown primary (1-7%). Less frequently, primary brain tumours can invade the meninges and disseminate along the cerebral spinal fluid (CSF) pathways.[1,4,5]

Interestingly, the occurrence of LC could be influenced by therapeutic interventions. For example, it has been suggested that long-term survivors of HER2-positive metastatic breast cancer, with controlled systemic disease under trastuzumab, have a high risk (34%) of developing metastases in the central nervous system (CNS), where tumour cells could be shielded from the trastuzumab.[6] The second example is the piecemeal surgical resection of brain metastases, which is associated with an increased risk of LC

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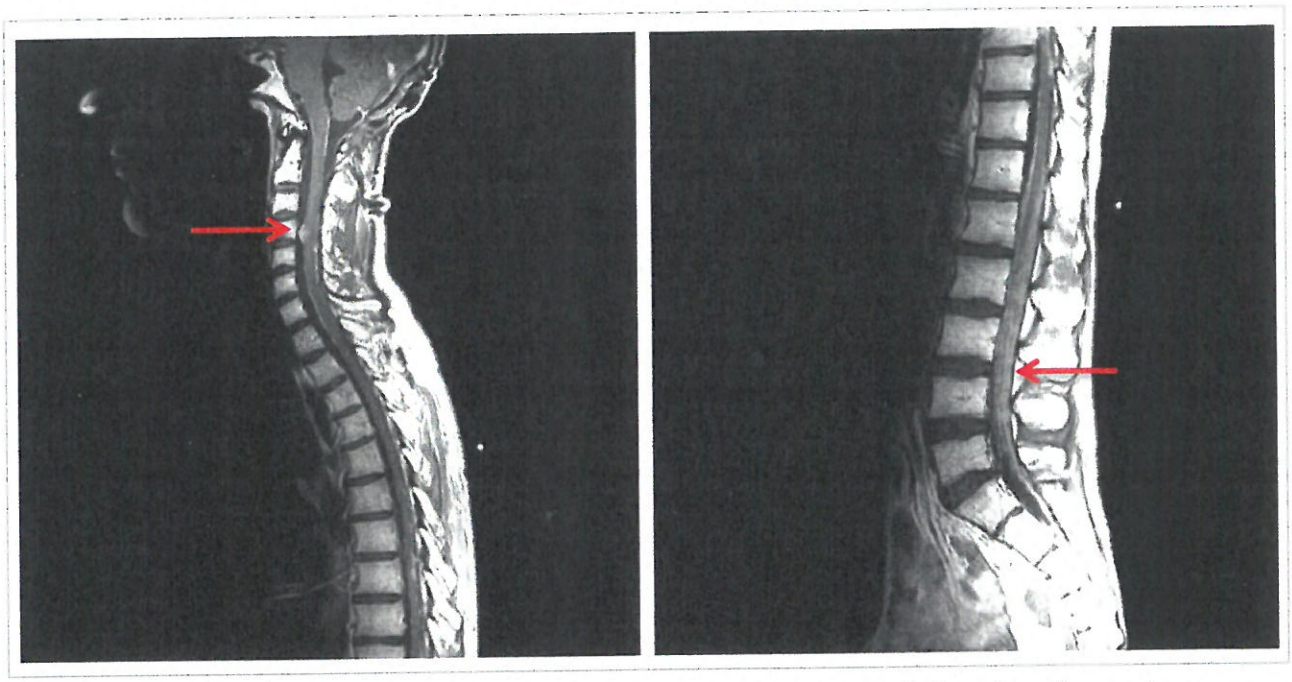

FIGURE 1. Magnetic resonance imaging of a patient with neoplastic involvement of spinal meninges (images from Medscape.org, 2012).

(hazard ratio of 4.08, $p < 0.01$), due to the spillage of tumour cells in the CSF.[7]

PATHOPHYSIOLOGY

The leptomeninges consist of the arachnoid and the pia mater. The space between these two layers contains the CSF and is named the subarachnoid space. In LC, tumour cells enter the subarachnoid space and are transported throughout the entire nervous system by CSF flow, causing either multifocal or diffuse infiltration of the leptomeninges.

Tumour cells can access to the CSF by 3 ways: (i) from the blood vessels in the arachnoid or choroid plexus; (ii) from a dissemination along perineural lymphatic vessels; (iii) or by direct extension from the brain or the skull.[1]

The most common sites of LC are the base of the brain in the posterior fossa, the Sylvian fissures and the cauda equina, probably due to the relatively slow flow of CSF through these areas and to the effect of the gravity.[1]

CLINICAL FEATURES

Symptoms of LC can be caused by different mechanisms: (i) by an indirect mass effect, leading to hydrocephalus and/or increased intracranial pressure (ICP); (ii) by the direct invasion of the brain parenchyma or a cranial nerve; (iii) or by the disruption of the blood brain barrier (BBB), inducing cerebral edema.[1]

Patients with LC present relatively acutely, over days or weeks, with multifocal and fluctuant neurological symptoms. However, around 25% of patients will remain completely asymptomatic. In symptomatic patients, the most common presenting symptom is headache, often triggered by changes in body position. Nausea and seizures are seen in 25% of patients. Less frequently, LC causes leg weakness (21% of cases, secondary to cauda equina invasion), cerebellar dysfunction (17% of cases, secondary to cerebellum infiltration), confusion or altered mental status (16% of cases, secondary to diffuse encephalopathy), or diplopia and facial weakness (14% of cases, secondary to cranial nerves invasion).[3]

NEUROIMAGING STUDIES

Gadolinium-enhanced magnetic resonance imaging (MRI) is the key exam for the diagnosis of LC. Sensitivity is relatively high, around 75%, providing that the exam assesses the entire craniospinal axis. Importantly, MRI should always be done before CSF sampling. In fact, lumbar puncture (LP), by decreasing ICP, will induce a meningeal thickening that mimics neoplastic involvement.[8,9]

The typical MRI findings include a diffuse or nodular meningeal thickening and/or contrast enhancement. Occasionally, a hyper-intense signal in the subarachnoid space on FLAIR sequences is found, due to the high protein content of tumour cells (*Figure 1*). However, all these findings are non-specific and other diseases might have a similar radiographic appearance (e.g. infectious or autoimmune meningitis). Moreover, in cancer patients, radiation therapy can also induce a nodular meningeal enhancement on the long term (*Table 1* - differential diagnosis).[10-13]

TABLE 1. Main differential diagnosis of LC.[11-13]

INFECTIONS	OTHERS	AUTOIMMUNE
Meningistic (bacterial, viral)	Post-radiotherapy	Vasculitis
Opportunistic (tuberculosis, cryptococcus)	Post-lumbar puncture	Sarcoidosis
Lyme disease	Intracranial hypotension	Granulomatosis (Wegener's)
West Nile virus		Langerhans cell histiocytosis
		Bell's palsy

CEREBRO-SPINAL FLUID ANALYSIS

CSF examination is the most useful laboratory test in the diagnosis of LC.

The presence of cancer cells in the CSF can modify each of its parameters. The CSF pressure is generally increased (> 200 mmHg in 57% of cases). A CSF pleocytosis can be observed, typically a lymphocytosis (39% of cases). Other CSF abnormalities include an elevated protein concentration (> 380 mg/L in 80% of cases), due to the BBB breakdown, and a low glucose concentration (CSF-serum ratio < 0.6 in 55% of cases), due to increased tumour metabolism.[3,14]

Ultimately, a definitive diagnosis of LC will only be made by the direct identification of tumour cells within the CSF. Unfortunately, the sensitivity remains limited and may require multiple CSF samplings. To minimize the risk of false negative results, it is recommended to withdraw a minimum CSF volume of 10 ml with each sample, to immediately fix CSF in an ethanol-based agent and to perform the puncture as close as possible to the suspected site of involvement. Repeated CSF samplings might be necessary because only 50% of patients with LC have positive CSF cytology by the initial CSF study. The yield is significantly increased by a second CSF study (75%), but little additional benefit is gained by subsequent CSF studies (2%).[14-16]

Despite all these recommendations, CSF cytology will remain negative in up to 10% of patients with clinically positive LC and, in this case, a typical MRI should be sufficient for the diagnosis and the potential treatment.[15,16]

TREATMENTS

In LC patients, the treatment goals include control of the neurologic function and extending the survival. If this is not possible, palliating symptoms is the goal.

Most untreated patients will die within 4 to 6 weeks. In treated and responding patients, the prognosis mainly depends upon the cancer type. Breast cancer patients experience the best treatment response and have a median survival reaching 7 months.[17] Obviously, the prognosis of LC is also influenced by the patient's condition: his Karnofsky Performance Status (KPS), the extent of the neurologic disease and the control of the systemic disease. To help physicians in their therapeutic decisions, the National Cancer Comprehensive Network (NCCN) guidelines have classified LC patients into two groups: good-risk and poor-risk patients (*Table 2*).[18]

POOR-RISK PATIENTS

Poor-risk patients are typically characterized by a KPS <60, multiple fixed neurologic symptoms and uncontrolled systemic disease. In this setting, a palliative approach should be considered. Targeted radiotherapy can be useful to relief symptoms caused by localised metastases and, nowadays, craniospinal irradiation is avoided due to its high toxicity profile. Corticosteroids may improve the headaches by decreasing ICP. Anticonvulsants drugs should be reserved only for patients with epileptic seizures and should not be used in the prophylactic setting. Finally, ventriculo-peritoneal (VP) shunting can be effective in case of hydrocephalus.[18]

GOOD-RISK PATIENTS

Less frequently, LC is diagnosed in patients with a good condition (KPS > 60), with minimal neurologic symptoms and effective systemic treatment options. In these patients, LC can potentially be treated more aggressively.[18]

The first step is to check and control the ICP. Elevated cranial pressure should be treated with corticosteroids. If corticosteroids are ineffective, VP shunting can be discussed, knowing that this procedure will definitively preclude the delivery of intrathecal (IT) chemotherapy and is associated with a risk of tumour seeding in the abdominal cavity.[19]

The second step is to perform a MRI- or radioisotope-CSF flow study to identify potential areas of CSF flow obstruction, which is seen in up to two-third of patients with LC. In this case, IT chemotherapy will not be homogenously distributed throughout the entire subarachnoid space, with a significant risk of decreased efficacy and increased

TABLE 2. Risk categories in patients with LC.[18]

Poor-risk	Good-risk
Multiple, fixed neurologic deficits	Minimal or no fixed neurologic deficits
Extensive systemic cancer without good treatment options	Effective systemic treatment of cancer possible
Encephalopathy or bulky CNS disease	

neurologic toxicity. Treatment of choice of CFS flow block is irradiation to the areas of obstruction, which is effective in 50% of patients with intracranial obstruction and only in 35% of patients with spinal obstruction.[17]

INTRATHECAL CHEMOTHERAPY

When the CSF flow is restored or normal, IT chemotherapy is the mainstay of treatment for LC in good-risk patients. IT chemotherapy is generally delivered through a subcutaneous reservoir connected to a catheter ending in the lateral ventricle. An alternative is to administrate the chemotherapeutic agents by multiple LP.

Compared to lumbar injection, ventricular administration of the chemotherapy offers several advantages. Firstly, LP is uncomfortable for the patient, it is time consuming and it is associated with a significant risk of epidural or subdural injection. Secondly, the concentrations in the ventricles and over the brain convexities are much more predictable if chemotherapeutic drugs are administrated via a ventricular catheter than by LP. Finally, in an observational study, a survival benefit has been suggested for intraventricular chemotherapy compared with lumbar IT chemotherapy. On the other hand, ventricular devices are associated with up to 10% of catheter-related complications, mainly due to Staphylococcus infection.[20,21]

In solid tumours, the drugs most commonly used for IT chemotherapy are methotrexate (MTX) and liposomal cytarabine.

MTX is a well-known anti-folate that is particularly active against breast cancer. The induction regimen consists of a fixed dose of 12 mg twice a week for 4 weeks. If clinical and cytological responses occur, the frequency of administration is decreased to weekly for 4 weeks, and then a maintenance regimen is continued monthly for a maximum of 6 months. A small amount of IT MTX will be released into the systemic circulation and can produce myelosuppression. Consequently, IT MTX is not recommended for patients with a platelet count < 50.000/mm^3. Multiple neurologic complications can also appear, principally aseptic chemical meningitis. This issue typically occurs within 2 days after the drug administration and can be effectively treated with a short course of corticosteroids.[22]

Liposomal cytarabine is a pyrimidine analogue, which is also active against neoplastic meningitis from solid tumours. Compared to MTX, liposomal cytarabine offers a similar clinical benefit but with a decreased frequency of administration (an injection every 2 weeks in the induction phase and every 4 weeks in the consolidation phase). However, this advantage is partially offset by an increased risk of chemical meningitis and, to minimize this risk, prophylactic dexamethasone is generally given.[22]

SYSTEMIC CHEMOTHERAPY

The superiority of IT chemotherapy over systemic therapy has not been proven in randomized controlled trials. On the other hand, due to the presence of the BBB, only a few chemotherapeutic agents achieve cytotoxic CSF concentrations after intravenous administration. For example, high-dose systemic MTX are necessary because of plasma to CSF gradient of 30 to one. Systemic MTX has showed clinical activity but objective responses are uncommon and the regimen is highly nephrotoxic.[23] In one small study, capecitabine has also induced long-lasting responses in 2 patients suffering from LC from breast carcinoma.[24]

TYROSINE KINASE INHIBITORS AND IMMUNOTHERAPY

Case reports of durable responses to EGFR and ALK inhibitors are available in mutated non-small cell lung cancers, especially with alectinib, a selective ALK inhibitor with excellent CNS penetration.[25,26] In malignant melanoma, BRAF inhibitors and ipilimumab have recently been demonstrated to be effective on leptomeningeal and brain metastases.[27,28] Intrathecal trastuzumab has also been tested in HER2-positive breast cancer, with objective responses observed in some patients.[29] Last year, a patient with craniospinal neoplastic meningitis, caused by a recurrent glioblastoma, has showed a complete response after intraventricular delivery

KEY MESSAGES FOR CLINICAL PRACTICE

1. Leptomeningeal carcinomatosis is a terminal and devastating complication of solid cancers.
2. Symptoms are mostly multifocal and fluctuant.
3. Diagnosis is mainly based on imaging (MRI of the entire neuraxis) and CSF analysis.
4. Since no effective treatment is available, inclusion in a clinical trial remains the best therapeutic option.

of a chimeric antigen receptor (CAR) T-cell therapy, a form of immunotherapy.[30]

CONCLUSION

Globally, IT chemotherapy induces a response in 27% of patients and results in a median survival of 14 weeks. Only 20% of patients will respond to radiation therapy. Combined IT chemotherapy and radiotherapy achieves a response rate of 34%, with no survival advantage. Median response rates of 67% are reported for intensified treatments, combining radiotherapy, intrathecal and systemic chemotherapy, but the median survival remains extremely modest.[22]

In conclusion, LC from solid tumours is a terrible and difficult to diagnose disease. Currently, only 7 randomized control trials are available in the field, with contradictory results. In future years, with the increase in long-term cancer survivors, medical oncologist will probably see more and more CNS metastases and we need to think how to treat, or even prevent, this difficult disease.

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