The diagnostic and therapeutic management of leptomeningeal carcinomatosis

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Introduction

The infiltration of the leptomeninges by malignant cells is not an uncommon complication of cancer and is called carcinomatous meningitis or leptomeningeal carcinomatosis (LC). Carcinomatous meningitis arises from either solid tumours or haematological malignancies.

In general, LC represents a devastating metastatic complication of systemic malignant disease with a dismal prognosis and increased mortality. The diagnosis is made by both lumbar puncture and radiological investigation, mainly magnetic resonance imaging (MRI). The most common associated malignancies are breast and lung cancer, melanoma, lymphomas and leukaemias [1, 2].

The therapeutic management of LC includes intrathecal administration of chemotherapy and radiotherapy. The treatment of LC remains controversial and no straightforward guidelines exist in the literature. The present article reviews the incidence, pathogenesis, clinical presentation, diagnosis and treatment of LC in all malignancies.

Incidence

LC was first reported by Eberth in 1870 [3]. Three to four decades ago LC was considered an uncommon manifestation of malignant disease. During the past few decades the incidence of LC appears to be increasing as imaging studies improve and as cancer patients live longer. Overall, neoplastic meningitis occurs in 5–8% of patients with cancer, whereas almost 20% of patients with neurological symptoms and signs are found to have LC during autopsy. Among solid tumours adenocarcinoma is the most predominant histological type. LC is more frequently seen in widely disseminated and progressive disease [4–8].

Breast cancer is the most common solid tumour complicated by LC and accounts for 11–64% of all cancer patients, but only 5% of patients with breast cancer [9–11]. Similarly, lung cancer accounts for 14–29% of all cancer patients, but only 9–25% of patients with LC [12–14]. For melanoma patients the numbers are 6–18% and 23%, respectively [15].

Sporadic cases of other solid malignancies such as head–neck, cervical, ovarian, renal and bladder cancer have also been reported [16–21]. Relapsed acute leukaemias or non-Hodgkin’s lymphomas as well as some paediatric tumours, i.e. embryonal rhabdomyosarcoma or retinoblastoma are also prone to develop LC [1, 22–24].

Pathogenesis

Anatomically, both the brain and the spinal cord are covered by the meninges. The meninges consists of the dura mater, the arachnoid membrane and the pia mater. The leptomeninges comprise the arachnoid membrane and the pia mater. The space separating the arachnoid membrane and the pia mater is referred to as the subarachnoid space, which contains the cerebrospinal fluid (CSF) [2].

The two most common pathways by which cancer cells can reach the leptomeninges are either by haematogenous and lymphatic spread or by direct extension from pre-existing malignant lesions.

With haematogenous or lymphatic spread both leukemic and solid tumour cells migrate through the arachnoid vessels or choroid plexus to the surrounding adventitia and extended to the cerebrospinal fluid. They fill the Virchow–Robin spaces around the cerebral blood vessels, they extend perivascularly, they involve the perineural and perivascular lymphatics and ultimately the endoneural and perineural sheaths of the intervertebral foramina [25–28].

With direct extension the tumour cells reach the leptomeninges from a pre-existing primary brain tumour (i.e. ependymoma and medulloblastoma) or from brain metastases (i.e. small-cell lung cancer) or from adjacent tumours along the cranial nerve pathways to the CSF (i.e. head and neck carcinomas) [16, 29, 30].

In addition, surgical extirpation of solitary brain metastases has also been implicated in the seeding of tumour cells to the subarachnoid space [31]. Once tumour cells enter the CSF, they can spread along the meningeal surface to distant areas of the central nervous system.

Differential diagnosis

The differential diagnosis of LC includes all states of chronic meningites, which are characterized by a subacute progressive leptomeningeal disease with persistent CSF abnormalities (elevated protein and pleocytosis) of at least 1 month’s duration.
The spectrum of aetiologies is associated mainly with infectious causes or cancerous infiltration. Toxic meningeal reactions to chemicals such as anticancer drugs, antibiotics or analgesics are more rare conditions and have an acute onset. Also, other coexistent diseases i.e. sarcoidosis, autoimmune disorders or vasculitides are extremely uncommon.

In immunocompromised cancer patients, i.e. lymphoma patients, chronic corticosteroid administration or patients undergoing bone marrow transplantation, the most common chronic infectious meningitis include bacterial (tuberculosis, listeriosis, brucellosis), fungal (cryptococcosis, candidiasis, coccidiomycoses, histoplasmosis) or viral (cytomegalovirus, varicella zoster, Epstein–Barr, herpes simplex) infections (Figure 1). Meningeal reaction to parenchymal brain abscess or parameningeal abscess is another rare infectious cause of chronic meningitis [1, 2, 32].

The differential diagnosis of chronic meningitis should be based on the medical history and clinical picture as well as on the CSF findings and other specific laboratory tests.

### Clinical presentation

Clinical features of LC are caused mainly by the obstruction of normal CSF flow or by direct tumour infiltration. The clinical symptoms and signs are associated with increased intracranial pressure such as headache, mental changes or nausea and vomiting or are related to the infiltration of the nerves producing local neurological deficits [1, 2, 33–35].

Of 456 patients from eight studies in the literature the most common presenting features were cranial nerve palsies (75%), headache (66%), cerebral disturbances (66%), spinal nerves (60%), mental changes (45%) and limb weakness (44%). It is interesting that meningism accounts for only 21% of all clinical features. On the other hand, the commonest cranial nerves involved are the III, IV, VI and VII nerves.

Other signs and symptoms include stroke-like syndromes due to occlusion of pial blood vessels, seizures due to infiltration or brain parenchyma, and symptoms of encephalopathy through interference with CNS metabolism (Table 1) [7, 8, 36–41].

### Diagnosis

The diagnostic management of LC is based on the CSF examination with cytology and biochemical analysis as well as on the radiological investigation, mainly with MRI.

### CSF examination

Basically, CSF examination includes the fluid cytology, estimation of the opening pressure, as well as measurement of protein and glucose concentrations. The measurement of other biochemical markers is less reliable.

Lumbar puncture for CSF cytology remains the standard diagnostic procedure. The demonstration of malignant cells in the CSF is still the cornerstone of the final diagnosis. An adequate sample of 5 ml or more increases the percentage of positive examination.

A positive CSF cytology is found on the initial lumbar puncture in 50–70% and in nearly all cases after three attempts. False-positive cytologies are associated with
infectious or inflammatory diseases demonstrating reactive lymphocytes.

Increased CSF opening pressure is found in 50–70% of the patients and depends on the extent of the leptomeningeal involvement. Elevated CSF protein and low glucose are observed in approximately 75% and 40% of the cases, respectively [12, 42–45].

A variety of other biochemical markers have also been studied in patients with LC but their use has poor sensitivity and specificity. Among these substances are the carcino-embryonic antigen (CEA), lactate dehydrogenase (LDH), alkaline phosphatase, β-human chorionic gonadotropin (β-HCG), creatinine kinase, monoclonal immunoglobulins, β-glucuronidase, β2-microglobulin, HMFG1 antigen, tissue polypeptide antigen, vascular endothelial growth factor, myelin basic protein, cathepsin B and H, cystatin-c and gastric releasing peptide [1, 2, 46–65].

Nevertheless, the gold standard of LC diagnosis remains the combination of the full clinical picture and positive cytology.

**Neuro-imaging studies**

Any cancer patient with clinical findings suggestive of LC requires an initial contrast enhanced computed tomography (CT) scan of the brain and cord in order to rule out brain metastases and to estimate the risk of herniation following lumbar puncture. Less than 20% of the patients will have a normal CT scan, whereas the rest will be diagnosed with brain metastases, hydrocephalus or contrast enhancement of the cerebral sulci or cisterns.

To detect leptomeningeal metastases, gadolinium-enhanced MRI is more sensitive than CT scanning. The sensitivity of MRI is nearly 70% while that of CT scan is around 30%. The most common MRI findings consist of typical nodules in the subarachnoid and parenchymal regions, parenchymal volume loss and sulcal/dural enhancement. The differential diagnosis should include infectious, inflammatory diseases, trauma or subdural haematomas [41, 66–69].

CT-myelography is not indicated due to low sensitivity, whereas the value of FDG PET scan is still under investigation [70].

Figure 2 provides an algorithm for the diagnostic investigation of LC.

**Therapeutic management**

Chemotherapy and radiotherapy have been used in different modalities. Basically, the poor results achieved with current modalities led to the controversial management of these patients. It is of paramount importance that any treatment decision should be based on which patient is most likely to benefit from it. Therefore, several clinical parameters should always be taken into consideration such as performance status,
underlying malignant disease and previous responsiveness to antineoplastic treatment.

Due to the absence of standard treatment strategies, the present review will attempt to provide the existing data from the literature, along with novel therapeutic approaches and to form minimum treatment recommendations for the daily practice of medical oncologists.

**Systemic chemotherapy**

In LC, chemotherapy has been given systemically, intrathecally via lumbar puncture and intraventricularly via an Ommaya reservoir.

Since most patients with LC also have metastatic disease they are usually treated systemically. Clear data on the effect of systemic chemotherapy in LC are lacking. Intravenous administration of conventional doses of several cytostatics cannot adequately penetrate into the CSF. For example, the proportion of an intravenous dose of methotrexate that enters the CSF is only 3%. Therefore, high doses of systemically administered methotrexate, cytarabine or thiotepa are required to yield therapeutic concentrations in the spinal fluid [1, 2].

In general there is no evidence that systemic chemotherapy is superior to intrathecal administration of antineoplastic drugs.

**Intrathecal chemotherapy**

Intrathecal chemotherapy can be administered either by a lumbar puncture or intraventricularly through an Ommaya implanted subcutaneous reservoir. Intrathecal administration of cytoplastics is considered the most reliable method.

The advantages of the intraventricular route against the lumbar puncture procedure, are that it is associated with: painless procedure, more uniform distribution into the CSF as well as better responses and longer survival, at least in childhood leukaemias. However, the recorded disadvantages are less sensitivity in yielding positive cytology, higher CSF glucose levels and lower protein concentrations, 10% incidence of infections and catheter misplacement or occlusion [1, 2, 71–74].

The two most common drugs in use are methotrexate and cytarabine, whereas thiotepa is not widely used as first-line treatment.

Methotrexate is given in different schedules i.e. 12.5 mg intrathecally (i.t.) twice or three times weekly, 15 mg i.t. weekly with or without hydrocortisone or 15 mg i.t. daily for 5 days every 2 weeks with folinic acid rescue. Toxicity related to the administration of methotrexate includes seizures, acute chemical arachnoiditis with headache, nausea, vomiting and mental changes, subacute onset of motor or sensory abnormalities and delayed necrotizing leukopencephalopathy [4, 10, 75–77].

Although cytarabine is not an active drug in solid tumours, its use is mainly restricted to haematological or childhood malignancies. It is given at doses of 30 mg i.t. daily for 3 days or 50–70 mg i.t. weekly. Cytarabine is used as first- or

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**Figure 3.** Suggested algorithm for the management of LC (adapted from NCCN).
second-line treatment or in combination with other drugs [1, 2, 4, 71, 78, 79].

Despite some evidence it is still controversial whether the use of combination chemotherapy in LC is superior to single intrathecal drug administration [10]. Dae-Young et al. [80] in a comparative study of 55 patients showed that the combination of intrathecal methotrexate 15 mg, hydrocortisone 15 mg/m² and cytarabine 30 mg/m² twice a week, is superior to the administration of methotrexate alone. Statistically significant differences were found in cytological response (38.5% compared with 13.8%, \( P = 0.036 \)) and in median survival (18.6% compared with 10.4 weeks, \( P = 0.029 \)).

In addition, there is no clear evidence to support the view that the maintenance of intrathecal treatment in patients achieved neurological stabilization or improvement [81–83].

Novel agents

There are case reports where the intrathecal administration of gemcitabine or trastuzumab was found to be effective in patients with non-small-cell lung cancer or breast cancer [84, 85]. Also, responses after systemic administration of letrozole and tamoxifen have been reported in individual cases of breast cancer [86–88]. Similarly, a patient with prostate cancer and LC responded to hormonal manipulation [89].

Radiotherapy

Radiation therapy is usually combined with the administration of intrathecal chemotherapy. Whether radiotherapy is as effective as intrathecal methotrexate administration or whether the combination of radiotherapy and chemotherapy is better than a single treatment, is difficult to answer due to the absence of prospective randomized studies [1, 2, 7, 8].

When radiotherapy is suggested it is usually given at a dose of 3000 cGy over 10 fractions to the brain and/or to the symptomatic, bulky or obstructive sites.

Therapeutic recommendations

Due to the lack of randomized studies and especially of studies referring to one specific primary tumour, a standard treatment cannot be recommended.

Figure 3 provides a practical guide for the therapeutic management of patients with LC.

Prognosis

Patients with LC should always be categorized as good or poor risk patients. Good risk patients have a better chance of achieving higher responses or even longer survival.

The response rate of LC patients with solid tumours managed with intrathecal chemotherapy and/or radiotherapy is around 50%. Responses in leukaemias or lymphomas seem to be higher. Response is defined as the achievement of stable disease or remission of clinical picture, negative cytology and improvement of CSF biochemistry.

Despite the evidence of response, the prognosis of LC remains poor. For patients with solid tumours the median survival is around 8 weeks ranging from 4 to 11 weeks. Patients with haematological malignancies, childhood tumours or chemosensitive solid malignancies may survive longer [1, 2].

References


