# Meningeal carcinomatosis in solid tumors

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## ABSTRACT

The involvement of the leptomeninges by metastatic tumors can be observed in solid tumors, in which case it is termed meningeal carcinomatosis (MC), and in lymphoproliferative malignant disease. It is more common in breast and lung cancer, as well as melanoma, with adenocarcinoma being the most frequent histological type. MC is usually a late event, with disseminated and progressive disease already present and, it is characterized by multifocal neurological signs and symptoms. Diagnosis is based on the evaluation of clinical presentation, cerebrospinal fluid and neuroimaging studies. The better systemic disease control is observed with new therapeutic agents, and the development of neuroimaging methods is responsible for the increasing incidence of such metastatic evolution. Intrathecal chemotherapy is generally the treatment of choice, although frequently palliative. Prognosis is guarded, although a higher performance status may indicate a subgroup of patients with a more favorable outcome.

Key words: meningeal carcinomatosis, cerebrospinal fluid, meninges, chemotherapy, metastases.

**Carcinomatose meníngea em tumores sólidos**

## RESUMO

O acometimento leptomeníngeo por metástases tumorais pode ocorrer em tumores sólidos, sendo chamado de carcinomatose meníngea (CM), e também em doenças linfoproliferativas. Tumores de mama, pulmão e melanoma são os principais responsáveis pelos casos, e adenocarcinoma é a histologia mais frequentemente encontrada. A CM é um evento tardio na evolução da doença e caracteriza-se por sinais e sintomas neurológicos multifocais. O diagnóstico se faz pela avaliação conjunta do quadro clínico, neuroimagem e estudo do líquido cefalorraquidiano. O maior controle da doença sistêmica obtido com as novas modalidades terapêuticas e a baixa penetração de drogas no sistema nervoso central, aliados ao desenvolvimento nos métodos de neuroimagem observado nas últimas décadas, são fatores que respondem por um aumento na incidência desta apresentação. A quimioterapia intratecal é o tratamento de escolha, porém, frequentemente paliativo. O prognóstico é reservado, sendo que o melhor *performance status* pode selecionar um subgrupo de pacientes com melhor evolução.

Palavras-Chave: carcinomatose meníngea, líquido cefalorraquidiano, meninges, quimioterapia, metástase.

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The involvement of the leptomeninges by tumor metastases was recognized first by the Swiss pathologist Karl Joseph Ebert in 1870[1]; the term meningeal carcinomatosis (MC) being proposed by Siefert (1902) to describe the clinical condition.

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It was considered rare at that time and the diagnosis was most commonly made *post mortem*[2]. In the last 40 years, it has been shown that 10% to 30% of patients with solid tumors develop neuraxis metastases, of which 4% to 15% represent MC[3,4]. Breast tumors, lung tumors and malignant melanomas are the principal tumors responsible for cases of MC. Adenocarcinoma is the most frequently encountered histological type[5].

In spite of accumulated understanding of the risk of MC and its clinical presentation, the occurrence of this condition remains underestimated in medical practice. Diagnosis is made difficult by the appearance of acute, subacute or late neurological changes due to the actual anticancer treatment; in many cases the initial investigations is limited to a cerebrospinal fluid (CSF) cytology, whose result often can be negative[6].

### Epidemiology

Meningeal carcinomatosis can be the first presentation of an as yet undetected primary cancer (6%-38%) or can occur during oncological treatment. The frequency of MC is estimated at 2% to 5% in breast cancer, 9% to 25% in lung cancer and in up to 23% of melanoma patients. There are indications that MC is a relatively late event in the evolution of solid tumors[3,7,8]. The better control of the systemic disease with newer therapeutic agents and poor penetration of these drugs into the central nervous system (CNS) are factors responsible for the increase in isolated relapses in the neuroaxis[9-11]. New forms of treatment for breast cancer, for example, such as taxanes, trastuzumab, and aromatase inhibitors have all contributed to the increased survival of these patient[12], but at the same time the observation of cerebral metastases as well as MC as the initial site for recurrent disease has become more common[10,13].

### Physiopathology

MC is a heterogeneous clinical entity from the neuropathological viewpoint, with differences between isolated MC, MC with invasion of the parenchyma of the CNS, and MC disseminated over the ventricular surface. From the clinical perspective it is more relevant to know the nature of the primary tumor (leukemia, lymphoma, or solid tumor) as well as the stage of the disease in which MC is diagnosed—as an isolated relapse, together with mild systemic disease, or in the context of widely disseminated metastases.

The meningeal involvement by the tumor can be due to hematological invasion of the subarachnoid space or cerebral ventricles, with later spread to the CSF, as happens in germinomas, ependymomas, retinoblastomas, optic nerve gliomas, pilocytic astrocytomas, and primitive neuroectodermal tumors. Conversely, the tumor may go directly to the dura mater, pia mater, or the ependymal structures, allowing for local tumor growth, as happens in nasopharyngeal carcinomas, cranial osteosarcomas, superficial cortical cerebral metastases, and in bony metastases with epidural invasion. Direct extension can also occur from tumor deposits and/or centripetal migration of tumor cells by the perineural and perivascular spaces, or following the cranial or radicular nerve pathways, as in adenocystic carcinomas[14,15]. This mechanism seems implicated as well in MC associated with the use of bevacizumab for the treatment of lung cancer[16]. The distribution of the leptomeningeal lesions is influenced by the CSF circulation, being more common in the lumbar region where the CSF flow is reduced.

### Clinical presentation

Symptoms of MC result from multiple interrelated events: obstruction of CSF flow causing hydrocephalus; neuronal dysfunction due to the metabolic competition between the tumor cells and normal cells for nutrients; neoplastic invasion of the Virchow-Robin spaces; and vascular alterations caused by the tumor growth itself. Typically there are multifocal neurological symptoms and signs at multiple levels of the neuraxis. Strictly speaking, the meningeal involvement can be classified into lesions of the cerebral hemispheres (present in 15% of patients), lesions of the spinal medulla (60%), and lesions of cranial nerves (35%)[15].

The complaints of the patient are usually the first clue to the subarachnoid invasion by tumor cells. Published case series have not shown that different types of cancer present differently. There has been consensus as regards the multifocal aspects (cerebral, cranial and radicular nerve involvement) in the clinical history and physical exam[14,15].

Initial symptoms include headache, nausea and vomiting, convulsion, lower back pain, radicular nerve pain, paresthesias, gait disturbances, and defects in mental functioning. In a recent series of 60 patients with MC associated with breast cancer, 55% of patients had headache, 50% had cranial nerve paralysis, 23% had intracranial hypertension, 20% had vertigo and 12% had convulsions[13].

Involvement of the cerebral hemispheres can be accompanied by headache, with nausea, vomiting and vertigo. Eventually, it can lead to complex dysfunction of the cerebral trunk, ophthalmoplegias, cerebral infarcts, and diencephalic syndromes[14]. Nuchal rigidity is infrequent (15% of cases) and the presence of signs such as aphasia, hemiparesis, or visual alterations are also described[14,15]. While mental changes, memory loss, cognitive disturbances, psychiatric disturbances and convulsions may be present, focal isolated defects are rare. Non communicating hydrochephalus is uncommon.

Signs and symptoms of cranial nerve involvement

are commonly found on the initial exam and tend to progress with advancing disease. Most common symptoms are diplopia, hypoacusia, amaurosis and facial hypoesthesia. Generally there is variable involvement of the optic nerves, the oculomotor, trochlear, trigeminal, abduscens, facial and hypoglossal nerves; vestibulocochlear nerve involvement is rare[17-19]. Dysfunction of cranial pairs in patients with cancer is not necessarily associated with MC, and lesions of the cranial base; soft tissue metastases, extra cranial infiltration of nervous structures, collateral effects of anticancer therapy, and paraneoplastic syndromes should be considered in the differential diagnosis.

Gait alterations can be caused by cerebellar dysfunction or by peripheral caudal equinal lesions. Involvement of the lumbosacral nerve roots is common in MC, and brings with it variable motor deficits. On examination, dysfunctions of the inferior motor neurons with muscular weakness, accompanied by loss of reflexes and hypoesthesia in the corresponding dermatomes are often observed. In a few cases, a mono or oligosegmental distribution can mimic degenerative diseases of the intervertebral discs, confusing the diagnosis. The symptoms may suggest a cauda equina lesion with flaccid paralysis and walking difficulties. Intestinal dysfunction and neurogenic bladder are findings infrequently found in MC. Signs of radicular involvement include arreflexia, asymmetry of nerve root involvement, muscular weakness, atrophy, paresthesias and dysesthesias[14]. Signs and symptoms of oligoradicular cervico-braquial nerve involvement can occur in breast cancer, initiated by radicular dysesthesias followed or not by painful paresias of the mononeuritic type. In the thoracic region, the most common finding involves bilaterally irradiating pain, often associated with local bony destruction. Multiradicular involvement is uncommon in solid tumors, but occasionally present as a painful ascending paralysis, similar to acute polyradiculopathy, a pattern also found in leukemias and lymphomas.

### Additional examinations

The diagnosis of MC is made by the combined picture offered by the clinical examination, neuroimaging studies, and CSF results[20]. The presence of neoplastic cells in the CSF is the most useful finding to confirm the diagnosis. Although this finding in the initial examinations has no prognostic value[6,21] it is a very important finding after treatment[21]. Nuclear medicine studies are useful in treatment planning.

**Neuroimaging studies** – Computerized Tomography (CT) with contrast use and Magnetic Resonance Imaging (MRI) allow identification of the pathological processes involved in leptomeninges. MRI, due to its technical advantages, is considered the standard choice for patients with a clinical presentation suggestive of MC[21]. Nevertheless, in spite of the superiority of MRI over CT, both methods have a high false negative rate (MRI 30% and CT 58%)[22]. With the use of paramagnetic contrast, any irritating stimulus to the meninges can be identified by hypercaptation, either circumscribed or diffuse. This includes intradural infiltration by tumor, focal neoplastic infiltration, local isquemia, infection, inflammation, granulomas, venous thrombosis, radiotherapy-induced lesions, chemotherapy irritating stimuli, heavy metals, hypoxia, subarachnoid hemorrhage, and trauma[23,24]. However, there has been a suggestion the MRI is less accurate, diagnostically speaking, in patients treated systemically with bevacizumab, due to the biological effects of this treatment[16].

The anatomical and functional basis of the meningeal enhancement is due to the increased capture of contrast by the dura mater. This makes it more difficult to distinguish the leptomeningeal enhancement, except in areas of major collection of CSF fluid near the base of the cranium and the major fissures. As the dura mater is thick, contrast medium does not penetrate the subarachnoid space up to the leptomeninges; thus any enhancement of the arachnoid and pia mater is pathologic. Penetration of the CSF barrier is a sign of advanced disease, and tumor invasion of the arachnoid villae is associated with CSF circulation disturbances. The ensuing reduction in its reabsorption results in communicating hydrocephalus, which should be considered as an indirect confirmation of MC

In the oncologic patient with clinical suspicions of MC, MRI findings will confirm or establish the diagnosis of MC. Suggestive findings include: nerve thickening, linear enhancement of the leptomeninges, superficial multiple cerebral metastases, and intradural nodules. Nevertheless, in patients without a previous diagnosis of cancer, who present a meningeal or subarachnoid space enhancement, MC is a possible diagnosis, and these findings require a pathologic diagnosis. Neurosarcoidosis, neuroschistosomiasis, chronic meningitis, Gullain-Barre syndrome, and previous lumbar puncture can also produce gadolinium enhancement of MRI. In the case of CSF lumbar punctures, a linear enhancement may occur not only at the puncture site but also along the neuroaxis, lasting for weeks to months, accompanied by headache due to low CSF pressure in some patients. Thus, patients suspected of MC should have neuroimaging exams before the CSF lumbar puncture, which will avoid artifacts on the exam.

**CSF cytology** – Demonstration of neoplastic cells in the CSF is moderately sensitive for the diagnosis of MC, but 15-20% of suspected clinical cases will not be confirmed by this method. Positive cytology for can-

cerous cells will increase with the number of punctures, but the false negative rate is still high, due to the similarity between tumor cells and ependymal cells, contamination by blood due to multiple puncture, few tumor cells in the collected specimen and inadequate preparation of the sample. It must be remembered also that when the tumor infiltration is confined to the cranium and the dura mater, neoplastic cells will not be found in the CSF.

Two cytological patterns may be seen with variable overlapping between them: the first consists of the presence of groups of cells which occasionally allow for the histological identification of the original tumor as seen in primary cerebral tumors (medulloblastoma, ependymomas, glioblastomas and pineoblastomas) and isolated metastases from solid tumors. The second type is characterized by isolated tumor cells with minimal aggregation, without characteristics of the original tumor architecture, such as seen when there is extensive involvement of the subarachnoid space. In these cases, the CSF cytology is useful only for confirmation of the presence of neoplastic cells, and does not serve for histological definition. Leukemia and lymphoma cells retain original characteristics of the tumor and the severity of the disease is not reflected necessarily in the CSF cellularity, which can vary from normal to very elevated.

Viral infections of the CNS can produce false positive cytology often making the distinction of lymphomatous infiltrations difficult, which does not happen in carcinomas or melanomas. Technical aspects which influence the cytomorphologial exam of the CSF should also be considered. It is preferable that the specimen be processed within an hour after collection. Cytocentrifuge use or sedimentation methods allow for better retrieval of cellular elements without artifacts[25,26]. Staining by May-Grünwald-Giemsa, usual in hematology, has advantages over the Papanicolou stain in terms of delineating nuclear structures and cytoplasmic limits, and thus is the method of choice. Mitotic figures and polyploidy are helpful in differentiating neoplastic cells and normal ependymal cells eventually present. However, their presence is neither a necessary nor sufficient diagnostic criteria in all cases. In epithelial tumors, usually the presence of few cell groups with their typical aspects is sufficient to confirm the diagnosis of MC. Moreover, in children, the presence of proliferative cells in groups is not always evidence of malignancy.

In patients with MC, only 50% will present initial positive cytology, but this will increase to 90% positivity after the third exam. As well as the repetition of the exam, CSF collected at different levels of the neuraxis could be helpful in obtaining a cytological diagnosis. Noteworthy, a CSF protein levels can vary according to puncture site (lumbar or suboccipital) even in the absence of CSF ob-

struction[15]. A low CSF glucose level (<60 mg/dl) and high protein level (>50 mg/dl) are additional parameters which contribute to confirming the diagnosis.

**Tumor markers** – The identification of biochemical tumor markers in the CSF with a potential diagnostic value has been a challenge. The following markers have been studied: beta-glicuronidase, lactate dehydrogenase 5, beta2-microglobuline, alfa-fetoprotein, carcinoembryonic antigen, carbohydrate antigen 15-3, prostate specific antigen, tissue polypeptide antigen, vascular endothelial growth factor, myelin basic protein, and the BB form of creatinine kinase[27-33]. Apart from being informative in a variable number of situations, none of these markers have definitely shown an increase in the diagnostic yield compared to the cytological exam.

The selection of tumor markers for use in CSF studies should be guided by the patient´s type of primary tumor, or by an observed serial elevation of these markers in the patient in question. The CSF marker of interest should be tested simultaneously with that of the serum, to eliminate the possibility of passive diffusion. When there has been no blood brain barrier (BBB) disruption, the penetration of tumor markers is minimal. Yet when the CSF marker levels are disproportionately high and the BBB is intact, the markers may be being produced in the subarachnoid space by the tumor metastases[34].

**Immunohistochemistry** – Monoclonal antibodies to mark tumors are not very helpful in solid tumors, due to the scarce cellularity and frequent dedifferentiation observed. However, in lymphomas and leukemias they may reveal the clonal nature of the lymphocytic infiltrates, without other malignant characteristics.

**Molecular biology** – Amplification of tumor specific gene sequences by polimerase chain reaction may be used to detect minimal quantities of neoplastic cells in the CSF, in situations in which conventional cytology is inconclusive[35]. This method can be used when the genetic alterations in the tumor are known, as in some forms of leukemais and lymphomas, but has no application in solid tumors.

**Nuclear medicine** – Flow studies of the CSF using radionucleotides (DTPA-Índio-111) are more sensitive than either MRI or CT in the anatomo-functional evaluation of the different CSF compartments. Its importance is well known in the identification of compartmentalization of the CSF and in obstructions to its flow. These findings are common in MC and critical in determining the distribution of CSF medications and also in the prognosis for these patients[36,37]. Radioisotope ventriculography is a secure, physiologic diagnostic method, based on the passive transport of the radiotracer by the ventricular system, subarachnoid cerebral and spinal space

About 50% of patients with MC will show alterations

in the CSF flow, most commonly at the base of the skull, cerebral convexities, and in the subarachnoid space of the terminal cone of the medulla and the cauda equina. It is thought that the compartmentalization of the CSF thus detected is due to the presence of small occlusions due to tumor fragments too small to be seen on MRI or CT[38].

### Treatment

Treatment of MC is frequently unable to provide lasting clinical benefit for the majority of patients. This is due to the limited scope of antineoplastic agents that can be administered safely by the intrathecal route, to extension of the basic disease and previous tumor exposure to antineoplastic agents with probable selection of chemoresistent clones, and the presence of flow obstruction of the CSF. Notwithstanding these problems, treatment can often alleviate symptoms with resultant increase in survival. The principal therapeutic modalities available in oncology, surgery, chemotherapy and radiotherapy, all have a part to play in the palliative treatment of patients with MC.

**Surgery** – Intrathecal chemotherapy can be administered by lumbar puncture or directly via intraventricular catheter. Patients with MC benefit from the implantation of a reservoir for intraventricular chemotherapy administration such as Salmon-Rickham and Ommaya devices, which can be safely implanted under general anesthesia or by local block, preferably with stereotactic techniques[39]. Use of reservoirs permits ambulatory treatment, which is more comfortable for the patient, permits the maintenance of treatment even with low platelet levels and assures that the medication is distributed most efficiently within the subarachnoid space. One comparative study of intraventricular versus lumbar delivery showed an advantage of the intraventricular delivery route, in view of time taken for drug diffusion into the CSF. This is particularly important when using drugs such as methotrexate, which have a short half-life[40].

A ventriculoperitoneal shunt for the symptomatic alleviation of intracranial hypertension, present in cases of communicating hydrocephalus may also contribute to palliation[5]. In this scenario, with intrathecal chemotherapy programmed, it is necessary to use a shunt with a valve to control the opening, such that it can remain shut for 6-12 hours after treatment to allow for diffusion and circulation of the medication.

**Radiotherapy** – Radiotherapy has a general and effective palliative role in the symptomatic control of MC. Pain, particularly radicular, can be rapidly alleviated with radiation treatment. It is administered in the symptomatic area of the neuraxis, occasionally including areas of major involvement as found on imaging studies, which are still asymptomatic

It is not uncommon for the symptoms to be worst in areas in which there is little radiological evidence for massive tumor involvement. Consequently, patients with pain and paresias in the lower leg need cauda equine irradiation, while those with alterations of the cranial nerves may require irradiation to the entire cranium or just to the skull base[41].

Focal palliative radiotherapy of the neuraxis can be done safely and effectively in short periods using a dose of 30 Gy in ten fractions. Although this treatment will produce a significant analgesic effect along with stabilization of the neurological deficits, neurological recover is unlikely. Autopsies have shown that even with destruction of the tumor cells, there still are lesions in the nerve roots and cranial nerves, either as demyelination and axonal lesion, resulting of treatment, or produced by the underlying disease process itself.

MC patients have widespread dissemination of tumor in the subarachnoid space, although they may have only focal symptoms. Palliative irradiation of the entire neuraxis, however, is rarely considered, due to its excessive hematologic toxicity, and to the fact that there is no proof to show that it can either prevent or retard neurological deterioration.

Palliative radiation therapy is best undertaken soon after the diagnosis of MC. In addition to indications for symptom control, radiotherapy can also be applied to CSF obstructions. This has been shown to be effective in restoring flow and allowing for a more adequate distribution of intrathecal chemotherapy, with resultant clinical benefit[37].

**Chemotherapy** – Intrathecal (IT) chemotherapy is one of the most commonly used treatments in MC. Theoretically its use gives the best exposure to the chemotherapy, because the impermeability of the BBB limits the availability of drugs delivered systemically. Some studies have suggested a better clinical outcome using intrathecal drugs such as methotrexate, cytaribine, and thiotepa. However up to 30% of patients were excluded from analysis as they did not have the functional capacity to receive treatment[42,43]. Patients with low functional capacity (defined here as ECOG >3 or Karnofsky <50%) do not benefit from palliative antineoplastic therapy[44].

Effective intrathecal chemotherapy presupposes a homogeneous passive diffusion of the agent along the subarachnoid space and ventricular system, giving good exposure of the tumor cells to the therapeutic drug levels. Patients with CSF flow alterations are most likely to have a therapeutic failure and thus a more guarded prognosis[43]. Reestablishment of adequate CSF flow seems to increase both the efficacy of the intrathecal chemotherapy and the prognosis[37]. The limited benefit of this type of therapy is due both to the poor penetration of

**Table.** Response rate and survival with intrathecal chemotherapy.

| Study | n | Response rate* | | Survival (weeks) | |
|---|---|---|---|---|---|
| Grossman et al.[47] | | | | | |
| MTX | 28 | 0 | | 15.9 | p=0.36 |
| Thiotepa | 24 | 0 | | 14.1 | |
| Glantz et al.[48] | | | | | |
| Liposomal ARAC | 31 | 8 | p=0.76 | 15 | p=0.15 |
| MTX | 30 | 6 | | 11 | |
| Hitchins et al.[49] | | | | | |
| MTX | 23 | 14 | p>0.1 | 12 | p=0.084 |
| MTX + ARAC | 20 | 9 | | 7 | |

*Neurological evaluation and/or CSF cytology. MTX: methotrexate; ARAC: Cytarabine; n: number of cases.

drugs into the tumor as well as to the limited armamentarium of therapeutic agents available. While it is possible that the anticancer agent may passively infiltrate a few millimeters into the tumors, this seems to be insufficient for a major cytotoxic effect[45].

Therapeutic protocols for MC use antimetabolites (methotrexate and cytarabine) with or without an alkylating agent (thiotepa)[43]. These antineoplastic drugs were introduced into clinical practice more than 50 years ago. They are moderately active for the treatment of neoplastic foci of leukemias, lymphomas, choriocarcinomas and breast cancer, although they are not considered effective for the majority of solid tumors[42,46]. In fact, there has been no report of superiority among chemotherapeutic agents in the past several decades. Table shows the response rates and survival times found in randomized studies which evaluated intrathecal chemotherapy use. Moreover, there is no unequivocal evidence to show that intrathecal chemotherapy gives the same increase in survival as that given by optimal systemic therapy.

The increasing number of patients with metastatic cancer who develop MC at some point in their disease gives good reason for investigation of regional chemotherapy with new antineoplastic agents. Promising initial results have been obtained using mafosfamide, lyposomal cytarabine, trastuzumabe, rituximabe, 5-fluoro-2´deoxiuridine, topotecan e nimustine[47-54].

Conventional systemic treatment has variable penetration in the subarachnoid space depending upon the extent of the breakdown of the BBB due to tumor implants and the subjacent inflammatory phenomenon. Regardless of the BBB drug penetration, data shows that systemic chemotherapy response has a positive impact on the survival of patients with MC[55]. A randomized trial compared intrathecal and systemic chemotherapy with systemic treatment alone in breast cancer patients with MC. The median survival was 18.3 weeks in the IT arm

and 30.3 weeks in the non-IT arm, although no statistical significance was achieved. Neurological complications related to treatment occurred more commonly IT arm (47% vs 6%)[56]. Despite a poor therapeutic index for use in solid tumors, methotrexate and cytarabine in high doses as used occasionally in high grade lymphomas and leukemias, give therapeutic CSF levels. This raises the question as to whether systemic chemotherapy should be considered a critical part of the multimodal approach of MC patients.

### Complications of treatment

The appearance of new sign and symptoms in a patient with MC is often a diagnostic problem, especially if the CSF cytology is negative. Recurrence, side effects of treatment and other complications are diagnostic possibilities which require different approaches.

Treatment, in general is safe. Adverse effects include headache, vomiting, mucositis and chemical meningitis. Late adverse events are seen in some patients who received intrathecal prophylaxis as a part of curative protocols. Collateral effects such as leukoencephalopathy, dementia and ataxia, may also occur frequently from neuraxis radiation.

Chemical meningitis secondary to intrathecal treatment can occur in 20%-40% of cases, and presents with headache, mental confusion, delirium and acute pain radiating into the extremities[47-49]. CSF exam cytology in these cases shows an increase in cellularity over 24 hours due to polymorphonuclear leukocytes. Use of concomitant glucocorticoids with the chemotherapy reduces the risk and intensity of the inflammation. There is a report of improving subacute myelopathy caused by intrathecal methotrexate when high doses of S-adenosilmethionine (200 mg, iv three times per day), folinic acid (20 mg, iv four times per day), cyanocobalamin (100 mg, once daily) and methionine (5 g, once daily orally) were supplemented[56]. Acute paraplegia is a rare complication described with use of triple therapy including methotrexate, cytarabine, and thiotepa. This clinical picture must be differentiated from subdural hematoma of the spinal medulla, a clinical condition which sometimes occurs in patients with MC. Other complications of intrathecal chemotherapy include infections at the puncture site, bacterial meningitis, and bleeding from a dislocated intraventricular catheter. Radiotherapy can produce a leukoencephalitis with acute or delayed symptoms. The risk for this complication is higher with the concomitant use of intrathecal methotrexate.

### Prognosis

Patients with MC have a guarded prognosis. Disease progression can occur a few weeks or months after

starting therapy, presenting as a worsening of initial complaints and neurological changes, and with new clinical symptoms and signs. Generally there is neuraxis involvement at multiple levels, with a rapid clinical deterioration and median survival of four to six weeks. Patients with malignant blood diseases generally have better clinical and functional capacities for a longer time and may be in remission with MC for months to years. Among solid tumors, breast cancer cases respond the best to treatment, with a median survival of six months[57-61]. The prognosis is determined by the extension of the systemic disease, resistance to therapy which occurs after multiple previous treatments, as well as progressive neurological dysfunction.

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