Anti-Tumour Treatment

Therapy of leptomeningeal metastasis in solid tumors

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A B S T R A C T

Leptomeningeal metastasis (LM), i.e. the seeding of tumor cells to the cerebrospinal fluid (CSF) and the leptomeninges, is a devastating and mostly late-stage complication of various solid tumors. Clinical signs and symptoms may include cranial nerve palsies, radicular symptoms, signs of increased intracranial pressure such as headache, nausea and vomiting, and cognitive dysfunction. In cases of suspected LM, the highest diagnostic sensitivity is provided by the combination of CSF cytology and contrast-enhanced MRI (cranial as well as complete spine). The therapeutic spectrum includes radiotherapy of the clinically involved region as well as systemic and intrathecal chemotherapy. The choice of treatment modalities depends on the type of LM (non-adherent tumor cells in the CSF vs. nodular contrast-enhancing tumor growth), additional systemic involvement (uncontrolled vs. controlled systemic disease) and additional involvement of the CNS parenchyma (LM as the only CNS involvement vs. LM + parenchymal CNS metastases). Larger contrast-enhancing nodular LM or symptomatic lesions of the spine may be treated with radiotherapy. In case of uncontrolled systemic disease, the treatment regimen should include systemic chemotherapy. The choice of systemic treatment should take into account the histology of the primary tumor. Intrathecal chemotherapy is most important in cases of LM of the non-adherent type. There are three substances for routine use for intrathecal chemotherapy: methotrexate, cytarabine, and thiopeta. Liposomal cytarabine shows advantages in terms of longer injection intervals, a sufficient distribution in the entire subarachnoid space after lumbar administration and improved quality-of-life. The role of new agents (e.g. rituximab and trastuzumab) for intrathecal therapy is still unclear.

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Definition and epidemiology

Leptomeningeal metastasis (LM) or leptomeningeal carcinomatosis, also referred to as carcinomatous meningitis or neoplastic meningitis, is defined by tumor cell spread to the leptomeninges and subarachnoid space. Within LM two different types of leptomeningeal tumor spread can be distinguished: (i) the first form is characterized by free-floating non-adherent cells or cell clusters without contrast enhancing nodular lesions in the subarachnoid space and/or with a faint growth on imaging (diffuse, non-adherent type). (ii) The second form of LM is characterized by contrast enhancing leptomeningeal tumor nodules (nodular type). LM can be found in solid tumors (leptomeningeal carcinomatosis and melanomatosis), hematological malignancies (leptomeningeal lymphomatosis or lymphomatous meningitis) and with primary brain tumors (e.g. leptomeningeal gliomatosis). LM is detected clinically in 5–8% of patients with solid cancer, and in 5–15% of patients with leukemia (e.g. acute lymphoblastic leukemia) and lymphoma (e.g. aggressive non-Hodgkin’s lymphoma such as Burkitt’s lymphoma) [1]. Results from autopsies indicate that LM is detected in about 20% of cancer patients presenting with neurological symptoms and in 8% irrespective of clinical symptoms [1]. However, the true incidence of LM is unknown, since this condition is probably clinically underdiagnosed. Based on an incidence for solid cancers of approx. 500 per 100,000, an incidence for LM of approx. 30 per 100,000 can be assumed. Other authors even estimate an incidence >400 per 100,000 [2]. The incidence of LM varies greatly depending on the histology of the primary tumor and...
depending on the cited references: malignant cells can be detected in approximately 5–8% of metastatic breast cancers [3–6], 9–25% of the lung [7] and in 6–18% of melanomas [8]. Especially for breast cancer, there is evidence of increasing incidence rates in the last years: this may be due to (1) predilection for the CNS by HER-2 positive tumor cells and/or (2) poor penetration of the CNS by trastuzumab or (3) improved visceral disease control leading to a longer life and onset of late tumor spread to the CNS [9]. Individual case reports of LM exist for virtually all systemic tumors. In the area of primary brain tumors LM is described particularly in ependymomas, medulloblastomas and primary central nervous system (CNS) lymphomas [10]. Even in gliomas (e.g. glioblastoma) evidence of LM is not rare: autopsy series suggest an incidence of approximately 20–25% [11,12]. A symptomatic dissemination is reported only in about 2% [13] and an overall diagnosis made by imaging or positive cerebrospinal fluid cytology in about 4% of patients [14,15]. However, breast cancer (27–50%), lung cancer (22–36%) and melanoma (12%) account for most cases in large series of this disorder [16].

LM usually occurs at a late stage of the disease and is often associated with a high systemic tumor burden [17,18]. With improved systemic tumor control through new drugs which do not penetrate the blood–brain barrier (BBB) or blood CSF barrier, the rate of parenchymal CNS metastases and LM may have increased since tumor cells may hide behind the intact BBB. Such a phenomenon has been described particularly for the HER2-positive breast cancers as mentioned above [9]. In 30–50% of patients also parenchymal brain metastases are found next to LM and the same number of patients has additional systemic metastases or progression of the primary tumor [18].

Symptoms and diagnosis

LM from solid tumors is probably underdiagnosed: in about 20% of all cancer patients with neurological symptoms LM can be diagnosed by autopsy, whereas in vivo the clinical diagnosis of LM can be successfully made only in 5–8% of patients with solid tumors [18,19]. Irrespective to clinical symptoms the rate of LM revealed by autopsy is about 8% in a series of 2375 patients [20].

Since the tumor cells can spread along the CNS, any neurological symptom can be associated with LM. Typical symptoms are radicular pain, cranial nerve deficits, headaches and back pain, visual disturbances, diplopia, hearing loss and neurocognitive syndromes. In advanced stages, also symptoms due to elevated intracranial pressure can occur such as headache, nausea/vomiting, and somnolence. An overview is given in Fig. 1.

In case of suspected LM from a solid tumor, a cranial and a spinal MRI with contrast medium (CM) and a lumbar puncture should be performed. A diagnosis of LM solely on clinical grounds is uncertain and usually not sufficient for the initiation of a specific therapy of LM. In the presence of LM, enhancing lesions of the leptomeninges are only found in approximately 70–80% of the cases (Fig. 2 shows typical MRI findings) [21,22]. MR imaging should - if possible - be performed before CSF analysis since a lumbar puncture can cause a transient meningeal enhancement and can thus complicate the interpretation of the scans (though the risk is only about 1% in the absence of post-lumbar-puncture headache [23]). A clearly identifiable contrast-enhancement along the cranial nerves or nodular accumulations along the spinal roots of the cauda equina are in the context of a known (systemic) tumor disease sufficient to make the diagnosis of LM, even in the presence of a negative CSF. A holospinal MRI may also provide additional evidence for obstruction of CSF circulation. In this case, an intrathecal chemotherapy is contra-indicated due to the risk of increased toxicity. Furthermore, the prognosis of patients with a disruption of the CSF flow is worse because the intrathecal chemotherapy does not reach all CSF compartments and this may be one of the reasons for treatment failure [24,25]. In North-American countries, further recommendations include the additional performance of an 111-indium- or 99-technetium-ventriculography for a more accurate diagnosis of the CSF flow. This examination is not (yet) routinely performed in Germany.

Regardless of the imaging finding the diagnosis of a LM can also be made solely by the detection of tumor cells in the CSF. Nevertheless, the MRI imaging should not be omitted, since the choice of therapy depends on whether only a diffuse, non-adherent leptomeningeal tumor spread is present or also nodular solid components can be detected (see below). Tumor cells can be found in the CSF in approximately 70–90% of patients with LM. In the case of a negative first puncture another puncture should be added: the sensitivity of cytology for detection of LM is for the first puncture at 50–60% and for the second at 85–90%. Each additional following puncture leads to only a slight increase (about 2%) of sensitivity [19,22,26].

To minimize false-negative findings, at least 5–10 ml of CSF cytological examination should be taken and analyzed within one hour. Intermediate cooling or fixation steps should be avoided. Other methods such as PCR, FISH and cytogentic studies may improve the diagnosis in some cases, but are not standard [27].

Considering the sensitivity of CSF cytology and MRI, it is important to note that both differ between LM from solid and hematological malignancies. A high sensitivity of MRI could only be
found in LM from solid tumors and for elevated CSF cell count. In case of hematological neoplasms and with normal cell counts, CSF-cytology was superior to MRI [22].

In addition to the cytological/neuropathological diagnosis, other CSF parameters are routinely investigated but are by itself not sufficient to make the diagnosis of LM: a moderate increase in cell number is found in approximately 63% of cases. A high protein and/or lactate concentration in the CSF may be regarded as indication for a high tumor burden in the CNS [21]. These parameters together with the cytological analysis are also used to monitor the treatment response. After successful therapy malignant cells should ideally not be detectable anymore and protein and lactate concentrations in CSF should decline. The determination of other CSF parameters such as creatine kinase BB (CK-BB), carcinoembryonic antigen (CEA), etc. are not part of the diagnostic routine due to their limited specificity. However, especially for detecting LM in adenocarcinomas there is some evidence for a high sensitivity of CEA (91%, [28]). The diagnostic value of the vascular-endothelial growth factor (VEGF) in the CSF is promising [21,29], but data are preliminary and not yet sufficient for routine application.

Prognosis

If left untreated, the LM of solid tumors leads to death within about 4–6 weeks [30]. With therapy, the overall survival is prolonged to 3–6 months. A response to therapy and a prolonged overall survival is observed especially in patients with breast cancer (median survival 7–12 months) [31,32], whereas patients with melanoma [33] or lung cancer (irrespective of EGFR mutation [34–36]) have a short median survival of approximately 4 months. Nevertheless, even for the latter an extended overall survival (>12 months) with therapy is possible in individual cases. The U.S. National Comprehensive Cancer Network (NCCN) defines patients with poor prognosis (so-called poor-risk group) [37] using the following parameters: low Karnofsky index (<60–70%), presence of severe neurological deficits, extensive tumor involvement with little opportunity to response to systemic therapy, additional parenchymal brain metastases and blockage of the CSF flow [24,25]. In addition, work of our own group identified the following adverse prognostic factors: older age >55–60 years, high CSF lactate and high CSF protein/albumin [21].

Treatment

Because there is a lack of prospective, randomized studies for leptomeningeal disease, most treatment recommendations are based on clinical experience or studies with a low level of evidence (Fig. 3). As mentioned above the diagnosis of LM in vivo can solely made in 5–8% of solid tumors: that is one reason for the lack of appropriate studies and also shows why clinical experience and expert opinions are so important.

Surgery

Surgical procedures play at best a marginal role in the treatment of LM. They are used for example for the implantation of a
reservoir for intrathecal administration of chemotherapeutic agents. In the case of a symptomatic hydrocephalus due to CSF circulation disturbances a ventriculo-peritoneal shunt can be implanted. Beyond this, in rare cases, the resection of large, space-occupying leptomeningeal metastases may be indicated (cerebral and/or spinal) or a biopsy of a leptomeningeal lesion in the context of a previously unknown primary tumor may become necessary.

Radiotherapy

In contrast to surgery, radiation therapy is an important part of LM therapy for some patients [38,39]. Usually, whole brain radiotherapy (WBRT) is applied in case of cerebral involvement and a focal radiotherapy for spinal lesions. The WBRT technique should ideally be 3D-based CT planning in order to fully include the retroorbital part of the eye socket and the cribiform plate [40–44]. Focal cerebral irradiation of individual regions is not established, but may be discussed in individual cases depending on the location. Patients with coexisting parenchymal (intracranial) brain metastases are treated primarily with WBRT. The WBRT should include the cerebral meninges, cribiform plate, base of skull, basal cisterns, and the spinal canal to the niveau of cervical vertebrae 1 and 2. Usually a dose of 30–36 Gy in fractions of 3 Gy is given, for patients with a better prognosis also 40 Gy in 2 Gy fractions can be given [45]. For patients with a short prognosis 5 × 4 Gy is an alternative to shorten the overall treatment time [46]. However, the very short survival time of many patients with LM even after WBRT challenges its generalized use: a recent study of 125 patients with LM from non-small cell lung cancer demonstrated no benefit of WBRT between patients treated with or without WBRT concerning survival [36]. Similar results are reported in another retrospective study for patients with LM from breast or lung cancer treated by WBRT with a median overall survival of 2 months [47]. However, only 27 patients were investigated in this retrospective study and no results concerning quality-of-life are reported. Interestingly the absence of cranial nerve dysfunction was significantly associated with a better survival. On the other hand, symptom control in patients with dysfunction of central cranial nerves due to larger leptomeningeal metastasis could be another indication for WBRT, although there is likely no benefit on survival especially in those patients [47]. In this context it is important to note that these and other cohort studies did not include quality-of-life measures that address the patients’ benefit e.g. from palliation of symptoms. Thus, the decision whether WBRT is indicated or not is still associated with some uncertainty. In patients with a positive CSF cytology but a low cerebral tumor load with only tumor cells lining the ventricular walls and without solid cerebral tumors, a WBRT may be withhold.

A craniospinal irradiation seems to be theoretically useful, since the entire compartiment of possible leptomeningeal tumor cell spread would be targeted. However, it is usually not carried out because of its pronounced myelotoxicity and increased burden for patients with LM and solid tumors. In the presence of spinal LM manifestations, irradiation should be restricted to symptomatic lesions or bulky disease in form of an involved-field local irradiation [46,48,49]. Patients with primary brain tumors such as medulloblastoma and ependymoma with LM are excluded from this restriction, since they do probably benefit from a craniospinal irradiation. In other tumors, there is no scientific evidence that irradiation of the craniospinal axis is superior to WBRT alone or a focal spinal irradiation [45].

In general, radiation therapy results in a rapid symptom control [48,50]. This makes focal spinal radiotherapy particularly beneficial for patients with a pronounced radicular pain syndrome and leads to a decreased use of additional pain medication [45]. In addition, radiation therapy leads to the restoration of CSF circulation in 30–50% of patients with a CSF flow disturbance [51] and can thus create the conditions necessary for intrathecal chemotherapy in these patients.

Systemic chemotherapy

In many patients with LM, systemic chemotherapy is indicated. In general, the choice of systemic chemotherapy should be made according to the histology of the primary tumor (see below). When connected to the blood circulation, the response of solid leptomeningeal metastasis to chemotherapy is comparable with metastases outside the CNS. For large leptomeningeal metastasis (especially for nodular – solid growth) sufficient efficacy is not expected from intrathecal chemotherapy, since the chemotherapeutic agents can penetrate only a few millimeters into the lesions (see below). In contrast, these large contrast enhancing nodular lesions without an intact blood brain barrier could be sufficiently targeted with systemically administered chemotherapeutic agents. Prospective, randomized studies are, however, not available.

[^36]: For spinal symptomatic lesions it may be useful to give radiotherapy for focal lesions. For an extensive form of nodular-solid meningitis, whole brain radiotherapy may be useful. Depending on the number and type of parenchymal brain metastases it may be decided to give whole brain radiation or focal radiotherapy only. In individual cases it may be useful to give radiotherapy for focal lesions. For an extensive form of nodular-solid meningitis, whole brain radiotherapy may be useful. However, this can may postponed of a potentially effective chemotherapy is available and only a low lesion load is present.
Single-arm studies or retrospective case series show that larger contrast-enhancing leptomeningeal lesions can be positively affected by systemic chemotherapy [21]. A systemic chemotherapy is also necessary in the presence of a relevant systemic tumor burden, which needs to be treated in addition to LM.

In addition, treatment with systemic chemotherapy itself is a significant positive prognostic survival parameter [21,52]. In a mixed group of patients, a recent retrospective analysis of 135 patients (73 with solid tumors) showed that the administration of systemic chemotherapy is associated with a longer survival time [52]. Furthermore, the entire therapeutic success of the systemic chemotherapy seems to depend on its ability to cross the blood–brain-barrier. It is important to note that many compounds for systemic application cannot penetrate the blood–brain-barrier and thus cannot reach the CSF if a sufficient concentration. CSF penetrating compounds are for example temozolomide, BCNU, CCNU, topotecan, capcitabine, lapatinib and in a higher dose also methotrexate (MTX). Accordingly, promising results were therefore first achieved with high-dose methotrexate therapy, in which sufficiently high levels in the CSF can be achieved. In 13 out of 16 patients complete CSF responses and a median survival time of 14 months were observed [53]. Compared to intrathecal monotherapy, improved survival times were achieved. However, mainly lymphoma and glioma patients and only a few patients with lung and breast cancer or melanoma were treated, so that no strong conclusions can be drawn for these tumors.

Among the few works dealing with systemic chemotherapy and LM of solid tumors, there are some reports on patients with melanoma, breast and lung cancer. Short-term stabilization in melanoma patients with nitrogenous [21] or a response to the BRAF inhibitors vemurafenib [54] or dabrafenib [55] have been described. However, vemurafenib and dabrafenib may hardly penetrate the blood–CSF barrier. With the exception of one case report [56] no studies with ipilimumab (CTLA-4 antibody) for LM are found in the literature. For patients with breast cancer a response to systemic tamoxifen therapy has been reported in individual cases [30]. In small cell lung cancer, responses were observed with high-dose etoposide therapy [57]. In patients with EGFR-mutated non small cell lung cancer good responses of leptomeningeal metastases were described for high-dose gefitinib or erlotinib [58–61]. CSF concentration of both tyrosine kinase inhibitors (TKI) may be insufficient when given at standard dose [62].

**Intrathecal chemotherapy**

Although intrathecal therapy is an essential part of LM therapy, its application cannot be recommended for every patient. The distinction between the two different leptomeningeal tumor spreading patterns described above has an impact on the indication for an intrathecal chemotherapy: (i) the intrathecally administered chemotherapy reaches the free-floating non-adherent tumor cells or cell clusters of the diffuse, non-adherent type well. A disturbance of the CSF flow does not exist. (ii) The nodular type is characterized by contrast enhancing leptomeningeal tumor nodules. It is important to note, that intrathecal therapy may probably not sufficiently reach malignant cells in tumor nodules with a diameter greater than 2–4 mm [63]. Therefore, intrathecal therapy is not indicated, when only the nodular type of LM is present. In this scenario systemic treatment should reach the LM tumor nodules well. However, frequently a combination of both LM types is present in patients so that a combined treatment approach is indicated. However, in general it is important to know that in two studies the absence of an additional intrathecal chemotherapy has no negative impact, as long as systemic chemotherapy is given [64,65]. Several limitation must be mentioned, however. In the work of Boogerd et al. [65] a substantial rate of neurologic complications were related to the ventricle catheter system (e.g. infections). Moreover, this trial was closed prematurely because of a dwindling accrual. In the trial of Bokstein et al. [64] two independent series of patients were documented prospectively but compared retrospectively.

**Chemotherapeutic compounds**

Three drugs are routinely used for intrathecal application: MTX, AraC (including the depot form of liposome-encapsulated AraC) and thiota. MTX is the drug for which the broadest experience in the treatment of LM exists.

MTX is a folic acid antagonist. DNA synthesis is inhibited by inhibition of dihydrofolate reductase, which provides reduced folates for purine synthesis. The liquor half-time is approximately 4–8 h. For this reason, a protocol has been established, where MTX is injected twice weekly for treatment induction and, when required, weekly for consolidation.

AraC and liposomal encapsulated AraC (DEPOCYTE®): as a pyrimidine analogue, AraC inhibits as well the DNA synthesis. Cytarabine is probably less effective for LM of solid tumors, but is well established for the treatment of lymphomatous meningitis. The conventional form of AraC should, similar to MTX and due to its likewise short CSF half-time, be applied twice weekly. For some time now a liposomal encapsulated formulation of AraC (DEPOCYTE®) is available. DEPOCYTE® must only be administered every 2 weeks. After a single injection of 50 mg sufficient cytotoxic CSF levels can continuously be measured for at least 14 days, and even lumbar administration of DEPOCYTE® results in a sufficient distribution in the entire subarachnoid space [66]. The implantation of a reservoir is therefore not necessary. Furthermore, the less frequent intervals of application of DEPOCYTE® compared to the other compounds is an additional benefit for the patients.

Thiotepa is an alkylating cell cycle-independent chemotherapeutic drug which is also available for routine intrathecal treatment, but is rarely used. It is recommended to apply 2 × 10 mg twice weekly (see Table 1).

**Routes of administration and devices**

Intrathecal therapy has the advantage that high drug levels in the CSF can be achieved with relatively low systemic side effects. An intrathecal therapy can be carried out in two ways. The chemotherapeutic agent may be brought into the CSF via an intraventricular Hickman or Ommaya reservoir or via lumbar puncture. A reservoir is a port catheter system, which is implanted by a neurosurgical intervention into a lateral ventricle (mostly right frontal). A lumbar application has the advantage that it is less invasive than the implantation of a reservoir system. Considering the poor prognosis of the disease and the uncertain role of intrathecal therapy due to missing prospective, randomized studies a lumbar application can be started without a preceding invasive surgery if an adequate substance is chosen. There are hardly infections observed with lumbar punctures, but have, however, been observed more frequently for reservoirs during the course of implantation or repeated injections. These advantages are, however, contrasted by doubts that a substance applied by a lumbar puncture with a usually relatively short liquor half-life time of a few hours (e.g. methotrexate (MTX) and cytarabine (AraC)) can uniformly be distributed over the entire subarachnoid space and thus reach all tumor cells in a sufficiently effective concentration. After an intraventricular injection higher cerebrospinal drug levels are achieved than after a lumbar injection [67]. This can lead to a longer progression-free survival time in particular when using the above mentioned chemotherapeutic agents with a short half-life time [68] or, as for breast cancer, to a better response rate and a longer overall survival time after intraventricular injection in comparison to lumbar application [69]. Another advantage of the use of a intraventricular reservoir is probably the safer
Protocols for intrathecal chemotherapy in LM.

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Note: Doses for lumbar application of methotrex and cytarabin are usually higher than for ventricular administration.

\(^1\) With administration of intrathecal methotrexate a leucovorin-rescue is necessary: calcium folinate 15 mg every 6 h for a period of 48 h.

\(^2\) To avoid chemical arachnoiditis begin administration of dexamethasone 4 mg p.o. or i.v. 2 \times daily for 5 days with start of DEPOCYTE\(^3\).

\(^3\) Dose for intraventricular application.

\(^4\) Dose for lumbar application.

administration of the chemotherapy. After a lumbar epidural injection both a CSF leak as well as accidental injections into the epidural space (10–15%) may cause local toxicity [70]. Furthermore, the puncture of the reservoir is less painful and there are no post-puncture complaints.

Beside a sole implantation of a reservoir there is also the possibility of an immediate implantation of a reservoir-on/off-ventri culo-peritoneal shunt (RO-VPS) in patients with a hydrocephalus. This is equipped with a so-called on/off valve, which allows for a simple mechanical interruption of the CSF flow. In addition to the shunt function, an intrathecal chemotherapy can also be applied. In a study by Lin et al., 24 patients with LM and hydrocephalus were treated in this way [71]: there was an improvement of the general condition in 83.1% of cases (41% lasting longer than 6 months), no shunt infection and only minor complications. 18 out of 24 patients received intraventricular chemotherapy, a cytological response was seen in 61.1%, with a median progression-free survival of 14 months and a median overall survival of 31 months. It was noteworthy that no cases of peritoneal carcinomatosis were observed and that the patients with RO-VPS compared to the control group survived significantly longer \((p = 0.008)\) [71]. Nevertheless, it should be mentioned that the implantation of a shunt system carries at least the hypothetical risk of spreading tumor cells \(\text{(e.g. peritoneal carcinomatosis)}\) in patients with LM. However, this is controversially discussed in the literature and some authors concluded that a CSF shunt does probably not predispose for an extraneural tumor spread [71–73]. Considering the pharmacokinetics of the intraventricular administered compounds, it is not clearly investigated if a RO-VPS may only prevent leakage of the intraventricular administered compounds, it is not clearly investigated if a RO-VPS may only prevent leakage of substances with a short half-life and if the administration of long acting compounds results in systemic (e.g. peritoneal) side effects. In the above mentioned study of Lin et al. [71] some patients received DEPOCYTE\(^5\) via RO-VPS. The authors observed no relevant toxicity.

**Efficacy and side effects**

Intrathecal therapy does not typically result in severe myelo-suppression or other specific cytotoxic side effects that are expected from systemic chemotherapy. Nevertheless, before starting treatment it is advisable to check that hemoglobin is above 10 g/dl, the neutrophil granulocytes are above 1.500/\(\mu l\), platelets are above 100.000/\(\mu l\) and the respective nadirs of prior chemotherapies are overcome. Especially when carried out in parallel to craniospinal radiotherapy, weekly laboratory tests appear useful, because the combination treatment can lead to myelosuppression in 5–10% of patients. However, a pronounced myelotoxicity is not expected in combination with WBRT.

MTX: most of the substances applied intrathecally remain largely within the CSF compartment. MTX, however, is slowly released into the serum. Therefore, the serum creatinine should be less than 1.5 mg/dl before initiation of an intrathecally MTX therapy and the implementation of a leucovorin rescue is recommended to avoid systemic side effects \((15 \text{mg/day every 6 h over 2 days})\). In 10–50% of cases a chemical aseptic meningitis \((\text{symptoms: headache, nausea, vomiting, photophobia})\) may occur after intrathecal chemotherapy; the symptoms usually last no longer than three days and respond well to oral steroids and/or NSAIDs [19,74,75].

Patients with LM from solid tumors did not benefit with prolonged survival or higher response rates from MTX combination therapies \((\text{e.g. MTX + Ara-C})\) compared to monotherapy [74], but could experience increased toxicity \((\text{MTX + Ara-C + thiopeta})\) [76]. In contrast to the treatment of LM from hematological diseases, intrathecal combination therapies \((\text{e.g. MTX, Ara-C, corticosteroid})\) are therefore not recommended in solid tumors. Not only for the combination of MTX with radiotherapy, but also for the MTX monotherapy it is important to remember that patients have a higher risk of neurotoxicity. Depending on age and survival time, an irreversible progressive leukoencephalopathy with severe cognitive deficits, incontinence, seizures, and focal neurologic deficits may occur [77,78]. A leukoencephalopathy after MTX occurs more often when given after than before radiotherapy. In a combined treatment schedule intrathecal treatment should therefore be given, if possible, for 2–3 weeks before whole brain radiotherapy. Should an intrathecal treatment in case of an insufficient CSF response during radiotherapy be indicated, a once weekly administration at the end of the irradiation week on Friday is recommended. Then, by beginning of the next irradiation on Monday the intrathecal MTX levels have dropped significantly again. Intrathecal treatment should be continued once weekly after irradiation since cytological CSF analysis revealed still malignant cells. Even Ara-C may lead to neurotoxic side effects such as leukoencephalopathy. However, the risk is probably lower than for MTX. The same applies to the combination of radiation therapy with thiopeta.

Ara-C and liposomal encapsulated Ara-C \((\text{DEPOCYTE\(^8\)})\): the drug is primarily approved for the treatment of lymphomatous meningitis. In a randomized study of 28 patients, a significantly better response \((\text{lipor stabilization, no neurological progression})\) has been shown as well as a longer median progression-free survival and median overall survival has been demonstrated compared with the conventional Ara-C [79]. In a randomized prospective controlled study in LM of solid tumors DEPOCYTE\(^8\) was compared with MTX in 61 patients [80]; with DEPOCYTE\(^8\) a similarly high response rate was found, but a significantly prolonged median time interval to neurologic progression as well as a trend for a longer LM-specific survival and a longer median overall survival. Another two single-arm prospective studies \((\text{mainly breast cancer})\).
The vast trial experience with DEPOCYTE® (>200 patients) is limited to the sole intrathecal chemotherapy without additional radiotherapy. A multi-center, international Phase I trial (DEP1501) to analyze the compatibility of DEPOCYTE® during and after radiation therapy was closed prematurely due to poor recruitment. Currently only the monocentric Phase I study (DepOR-aCe) in Bonn, Germany is recruiting patients with meningitis-melanomatosa to analyze the compatibility of DEPOCYTE® concomitant and adjuvant to radiotherapy. The combination of DEPOCYTE® and radiotherapy (concomitant radiochemotherapy with temozolomide and adjuvant temozolomide and then together with DEPOCYTE®) was successful in two case reports (one unpublished case) and without additional toxicity [83]. In a retrospective case series of patients with breast cancer and LM there was also no toxicity for the subgroup with combined chemoradiotherapy [5]. With regard to a combination of DEPOCYTE® and systemic chemotherapy first reports are available which show that the combination with high-dose MTX and/or AraC in patients with acute lymphoblastic leukemia or in connection with an allogeneic stem cell transplantation results in a high neurotoxicity rate (16%; transient encephalopathy/encephalitis, cauda equina syndrome) [84,85].

When using DEPOCYTE® it should be noted that an arachnoiditis or a conus medullaris-cauda equina syndrome can occur. In a retrospective case series in approximately 17% of the patients or 5% of cycles administered a chemical meningitis or a conus medullaris-cauda equina syndrome was observed [86]. With a strict use of dexamethasone for prophylaxis of arachnoiditis (with the start of DEPOCYTE® administration application of dexamethasone 4 mg p.o. or i.v. 2 x daily for 5 days) and an exclusion of patients with CSF flow disturbance, we see these complications significantly less frequently. In cases of arachnoiditis, systemic administration of high-dose corticosteroids (e.g. prednisolone, 1 g i.v. for 3–5 days) is suggested.

Thiotepa: in two earlier studies with small and not homogeneous patient groups (mainly lymphomatous meningitis) response rates could be observed with a cytological remission of about 40% each [87,88]. This does not differ significantly from the cytological remission rates of other chemotherapeutic agents. The comparable efficacy of MTX has been highlighted above.

Experimental approaches: in addition to the substances approved for intrathecal therapy, there are a number of experimental approaches. For mafosfamide [89], topotecan [90,91], etoposide [92] and gemcitabine [93] some initial data are available. Etoposide was at best moderately effective (response in 26–45%) [92]. Topotecan led to a CSF response in 10/14 patients, so that some effect can be assumed. However, it is worth noting that in this study mostly patients with primary brain tumors (11/14) were included [90]. Under gemcitabine significant neurotoxicity was observed in some patients, so that this drug does not appear suitable for intrathecal use [93]. Maybe one of the most promising experimental approaches for intrathecal therapy are currently the use of the monoclonal antibodies rituximab and trastuzumab. Rituximab, the anti-CD20 antibody is already used in the treatment of systemic B-cell lymphomas. In two small studies a cytological remission in 60–75% of patients was achieved with twice weekly application of rituximab [94]. Similar remission rates were also found after intrathecal administration of rituximab in combination with DEPOCYTE® [95]. Interestingly, a remission was achieved with intrathecal rituximab therapy also in some parenchymal or intraocular lesions. Trastuzumab is a humanized monoclonal antibody which is directed against the human epidermal growth factor receptor (HER-2, or ERBB2). Trastuzumab has been successfully used systemically in HER-2 positive breast cancer. There are no studies for the intrathecal administration of trastuzumab, but several case reports and one review which showed a response after intrathecal injection of trastuzumab [96,97]. Neurotoxicity was observed neither with intrathecal rituximab nor with trastuzumab.

**Treatment schedules**

Table 1 gives an overview of the practical use of these intrathecal chemotherapeutic drugs. However, due to insufficient data, it is neither possible to give a clear recommendation for an optimal dosing regimen nor for the indication of a maintenance therapy of the different drugs. Moreover, the possible cumulative neurotoxicity (especially with MTX) is another issue that might have impact on the duration of intrathecal therapy.

Treatment response is measured by the clinical course of the patient and by liquor parameters (see above). Therefore, with each intrathecal injection, cerebrospinal fluid should be taken and investigated [21]. Some centers recommend a cytologic complete remission of liquor within 2–3 weeks and, due to the only palliative treatment approach, a completion of intrathecal therapy after the detection of 2–3 CSFs with negative liquor cytology. Some, however, recommend a completion of therapy only after a treatment period of minimal 3 weeks. The clearance of CSF from malignant cells (cytological remission) is reached in up to 50% of patients with solid tumors [18,77]. In patients without cytological remission but stable liquor findings and a clinically stable or improved course, it may be advisable to continue the intrathecal therapy [83]. Some centers however, recommend to try a discontinuation of therapy after about four weeks of intrathecal treatment. Cessation of treatment is justified in case of a significant clinical deterioration due to LM, and not to additional parenchymal metastases. Termination of therapy may also be indicated in case of continuous deterioration of CSF cytology.

**Creating an individual treatment concept**

The therapeutic concept for LM is based upon the MRI pattern of leptomeningeal tumor spread: intrathecal chemotherapy is indicated for the diffuse, not adherent type (see above), while radiotherapy and systemic chemotherapy are preferably used for contrast enhancing leptomeningeal tumor nodules (nodular-solid type, see above) and/or the presence of parenchymal brain metastases. As mentioned above, however, it is theoretically possible that even in a nodular-solid form desquamation of single tumor cells and diffuse spread in the subarachnoid space can occur without being detected. However, a combination of both LM types is present frequently so that combined treatment approaches are indicated. Fig. 3 gives an overview and support for decision-making, taking into account these factors (according to [98]).

**Conclusion**

The LM of solid tumors is a form of CNS metastases with extremely poor prognosis. The symptomatology is characterized by cranial nerve disorders, radicular symptoms, and in advanced cases also signs of intracranial pressure (headache, nausea, vomiting, cognitive disorders, consciousness disorder). The contrast-enhanced magnetic resonance imaging of the whole CNS (spine and brain) in combination with the cytological CSF analysis confirm the diagnosis. Therapeutic decisions should take into account that LM patients often have additionally parenchymal CNS metastases and poorly controlled systemic tumors. Treatment options are radiotherapy of the affected area, as well as systemic and intrathecal chemotherapy, whereas the combination of these treatment methods depend on the type of leptomeningeal tumor spread (nodular-solid vs. diffuse, non-adherent), on additional disease of...
Conflict of interest

Niklas Schäfer, Frederic Mack, Martin Glas and Ulrich Herrlinger received honoraria from Roche. Martin Glas, Brigitta Baumann and Ulrich Herrlinger received honoraria from Mundipharma.

References


