Leptomeningeal metastasis in solid tumours: Is there a role for intrathecal therapy?

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Abstract

Leptomeningeal metastasis (LM) is a debilitating complication that usually occurs late in the course of metastatic disease in patients with solid tumours. Without treatment patients die within a median of 4–6 weeks due to progressive neurological deficit. Intraventricular chemotherapy with involved field RT is the standard treatment, but there is no clear evidence that such treatment improves outcome. Significant neurological complications occur in at least one third of the intensively treated patients. Because of disruption of the blood-brain barrier in LM, systemic therapy can also be effective. In non-controlled studies and in a randomised trial in patients with LM from breast cancer it was demonstrated that addition of intraventricular chemotherapy to systemic treatment and involved field radiotherapy did not improve outcome, but on the other hand adversely affected quality of life by its neurotoxicity. So, the value of intraventricular chemotherapy as the standard treatment of leptomeningeal metastases in patients with solid tumours still needs to be demonstrated.

Introduction

Leptomeningeal metastasis (LM), infiltration of tumour cells in the leptomeninges (pia and arachnoid) of the brain and spinal cord and in the subarachnoid cerebrospinal fluid (CSF) space is a relatively rare complication in patients with solid tumours that usually develops late in the course of metastatic disease. It is diagnosed with increasing frequency, most likely due to prolonged survival of patients with metastatic disease and because of improvement in diagnostic methods, and, in breast cancer patients, maybe because increased use of chemotherapy might lead to some increase of isolated central nervous system metastasis [1]. There is so far no evidence that isolated leptomeningeal metastasis develops more frequently in breast cancer patients treated with trastuzumab.

In about half of the patients with LM from solid tumours, breast cancer is the primary tumour (in particular lobular carcinoma with a reported incidence of more than 10%) [2,3]. Other common primaries are lung cancer (especially SCLC, with a 2-year cumulative incidence of 10%) [4,5], and melanoma, but LM may develop in any cancer [6–10]. The estimated incidence of LM as isolated central nervous system (CNS) metastasis in patients with breast cancer is approximately 3%. Post mortem studies report incidences of 5–>20% [11,12], but in those series LM is usually associated with other CNS metastasis, in particular brain metastases that usually will have dominated the neurological picture in the preterminal stage of metastatic disease. A post mortem study at the Memorial Sloan Kettering Cancer Centre showed LM as isolated CNS metastasis in only 1.9% of patients with CNS metastasis [13].

Leptomeningeal metastasis is notorious for its rapidly progressive and disabling neurological symptoms. If left untreated, patients with LM have an estimated median survival of about 4–6 weeks [14,15, 6]. Based on the favourable results achieved in LM of leukaemia, intraventricular chemotherapy combined with involved field radiation therapy (RT) as necessary became the standard treatment for patients with LM form solid tumours. However, efficacy of this intensive standard treatment in LM from solid tumours is disputable, and toxicity appears considerable. More recent data, including a randomised study in LM from breast cancer, indicate that intrathecal therapy as standard treatment for LM from solid tumours should be reconsidered.

Pathogenesis and pathophysiology

Tumour cells can reach the meninges or CSF space through different routes. Massive invasion through the

leptomeningeal vessels that frequently is the source of meningeal infiltration in haematological malignancies is not likely to occur in LM from solid tumours. It was suggested that malignant infiltration of the choroid plexus is the main source of tumour cells in the CSF but this was disputed by others [16,6]. Particularly in breast cancer and lung cancer, tumour cells may spread from bone metastasis in the spinal column via the perivascular spaces of the vertebral and radicular veins into the subarachnoid CSF space [17]. Other presumed but uncommon pathways are retrograde spread of tumours cells via the valveless Batson's venous system, by perineural invasion, or by invasion from a subdural, subependymal or (relatively rarely) cortical tumour mass [18,16,6]. Iatrogenic spread of tumour cells into the CSF was reported, particularly following resection of cerebellar metastasis [19,20], but the incidence of this complication may be overestimated [21]. Once the tumour cells enter the CSF, they are spread by CSF flow. To survive in this environment the cells adhere to nerve roots and the vasculated arachnoid, where they can grow to form macroscopic tumour plaques, sometimes attended by a local inflammatory reaction. This may cause obliteration of the subarachnoid space with CSF compartmentalisation and hydrocephalus. Adhesion to, and invasion of, nerve roots occurs mostly at the skull base and in the cauda equina. Parenchymal invasion in the brain and spinal cord occurs primarily via the perivascular space of the penetrating vessels, mainly in the cerebral cortex and the dorsal region of the spinal cord. Local compression of those vessels by the perivascular tumour rings can lead to ischemia and micro-infarctions. Further invasion of the parenchyma causes neurological deficit and sometimes seizures. Symptoms and clinical manifestations of LM are the result of focal or multifocal tumour invasion of nerve roots, brain parenchyma and/or spinal cord, cortical hypofunction or ischemia, meningeal irritation, increased intracranial pressure, and CSF flow disturbances including hydrocephalus [10,22,23]. Hydrocephalus is observed in approximately 20% of patients with LM and is nearly always of the non-resorptive type [24].

Diagnosis

Early diagnosis of LM is essential because clinical outcome is related to neurological dysfunction at the start of treatment.

Clinical diagnosis

Leptomeningeal metastasis usually presents late in the course of metastatic disease in conjunction with signs of tumour progression at other sites, including the CNS. Occasionally, LM is the first presentation of metastatic disease; this has been described in nearly all types of solid tumours. There are no clinical signs unique for LM. Multifocal symptomatology is typical for LM, and neurological examination usually uncovers more abnormalities than symptoms suggest. Symptoms are categorised as cerebral (incidence approximately 50%), cranial nerve (approximately 40%), and spinal (approximately 50%). Approximately half of all patients have symptoms that correspond with one of these three categories. However, neurological examination reveals that most patients have abnormalities in at least two of the three categories [24,6]. Most common symptoms are headache (incidence approximately 40%), confusion (30%), ataxia (25%), double vision (25%), radicular pain or palsy (25%) and nausea and vomiting (15%). Seizures occur in about 5% of patients. Meningeal irritation is found in 15% of patients. Cranial nerve palsy involve, in particular, the oculomotor, facial, trigeminal and vestibulo-acoustic nerves. Spinal symptoms occur primarily at the lumbosacral level; 15% of patients have sphincter disorders. Unsuspected brain metastases are present in about 25% in patients with clinical LM; this percentage is most likely higher in patients with small cell lung cancer and melanoma. It is unclear how often unsuspected LM occurs in patients with clinically overt brain metastasis. Leptomeningeal metastases were diagnosed in 15% of patients with clinically overt brain metastasis from breast cancer [25]. There appears to be no direct relationship between the presence of LM and epidural metastasis. The differential diagnosis is extensive and includes a variety of diseases such as metabolic disorder including liver metastasis and hypercalcemia, infectious meningitis and/or encephalitis, brain metastasis, dural metastasis, skull base metastasis, paraneoplastic disorders, intervertebral disk lesions and treatment related complications including the adverse effects of morphine, dexamethasone, RT and chemotherapy.

Diagnostic imaging

Gadolinium enhanced MRI scanning is the radiological method of choice when LM is suspected. A few studies have addressed the sensitivity and specificity of MRI with respect to LM. Similar results were reported in two studies conducted in patients with a primary solid tumour or haematalogic malignancy who were clinically suspected of having LM [26,27]. Sensitivity and specificity were both about 75%. Since there are no pathognomonic MRI hallmarks of LM

the specificity of LM is relatively low. The abnormalities on gadolinium enhanced MRI scans include meningeal or dural contrast enhancement, enhancement of intradural spinal nerves, subarachnoid nodules and superficial cortical enhancement indicative of parenchymal invasion [28,29]. Indirect characteristics include abnormal signal intensity of the CSF caused by substantial increase in protein concentration, spinal nerve thickening, spinal cord thickening, thickened hypophyseal stalk, and hydrocephalus. Similar MRI findings may occur in infections, inflammatory diseases like sarcoidosis, cerebrovascular complications, trauma, a recent epileptic seizure, but also a post lumbar puncture CSF hypotension syndrome.

CT scan is inferior to MRI for the detection of intracranial LM and is not suitable for the diagnosis of spinal LM. The CT hallmarks of LM are similar to those for MRI. The sensitivity of CT for detection of LM is approximately 35% and a specificity is similar to that of MRI (±75%) [30]. MRI and CSF cytology can be complementary for the diagnosis LM. In the study by Freilich and colleagues [26] in 137 patients clinically suspected of LM, the false negative rate for CSF cytology when MRI was positive was 36%; the false negative rate for MRI when CSF cytology was positive was 30%.

MRI evaluation can be limited to the symptomatic area of the neuraxis. If LM is demonstrated at the spinal level MRI brain might be considered to rule out subclinical brain metastasis, which could be relevant for further treatment planning. Although MRI is not highly specific it can be sufficient to establish the diagnosis in patients clinically suspected of LM, with a malignancy known for its propensity of meningeal seeding. If MRI or CT results are inconclusive or negative, CSF examination should be performed.

CSF analysis

Demonstration of tumour cells in the CSF is diagnostic for LM. A false positive CSF cytology is only sporadically found in the LM from haematologic malignancies, and is not found in patients with LM from solid tumours. CSF cytology is tumour positive at first lumbar puncture in about 50–80%, increasing to about 90% at second and following lumbar punctures. In 5–10% CSF, cytology remains tumour negative in patients with clinical, radiological and biochemical evidence of LM [10,31–34]. Cisternal CSF cytology may be more sensitive than lumbar CSF in patients with cerebral symptoms [35]. Because of the limited sensitivity of cytology a number of new techniques were developed to supplement classic CSF cytology, such as immunocytochemistry, PCR, flow cytometry and cytogenetic analysis [36–40]. These techniques help to increase the probability of gaining a positive cytology by few percentage points, but they do not replace classic cytology as primary diagnostic tool and, thus are considered adjuvant. In addition, assessment of specific and non-specific tumour markers in the CSF lack sensitivity and specificity compared with CSF cytology, but may be useful for monitoring the course of disease [41–43]. In particular vascular endothelial growth factor (VEGF) may be a useful marker for both diagnosis and prognosis [44,45]. The routine examination of the CSF should include measurement of the opening pressure, cell count, and measurement of CSF protein and glucose: abnormal findings are non-specific, but a completely normal routine CSF examination almost excludes LM [33,42,31,43]. A significantly decreased glucose is only found in infectious meningitis and in LM.

Treatment

In LM from solid tumours the primary intention of treatment is to improve or stabilise the clinical neurological condition, and secondly to prolong survival. In the majority of patients with LM, neurological deficit is either the cause of death or a major contributing factor. Usually there is also systemic disease progression that likewise has its influence on survival. In contrast to LM from leukaemia or lymphoma a complete and durable eradication of leptomeningeal tumour activity is not feasible and therefore should not be considered the goal of treatment [31,46]. Because neurological signs of LM are often disabling or rapidly become disabling, timely initiation of treatment is needed. Without treatment median survival is 4–6 weeks, and death usually caused by progressive neurological dysfunction. However, occasionally patients live considerably longer without specific treatment. In addition to supportive care, treatment options include local RT, intrathecal chemotherapy and systemic therapy. In general, treatment has varying effects on different neurological symptoms: response in terms of headache and radicular pain is often favourable, but improvement of confusion or fixed motor deficit is usually poor. A response to treatment usually occurs within the first 4–6 weeks of treatment [31,47]. A clinical neurological response seems a better parameter than the CSF cytological response for predicting the further course of disease [31].

Radiotherapy

For disabling symptoms, local RT can be given with a short palliative schedule such as 20 Gy in five fractions

or 30 Gy in ten fractions. Although the likelihood of reducing symptoms caused by LM, such as pain or functional loss has not been well documented, a favourable clinical effect is reported in 40–70% of patients [24,31]. Radiotherapy probably has no influence on survival [31]. Radiotherapy has the advantage of penetrating macroscopic meningeal tumour and parenchymal tumour infiltration that is not reached by intrathecal chemotherapy. Radiotherapy may also relieve CSF flow blocks, which influence efficacy and toxicity of intrathecal chemotherapy [48–51]. Successful relief of CSF blocks by RT is reported in about 50% [48,49]. In the palliative setting, RT of the entire neuraxis is too toxic and used only very rarely [52]. Intrathecal RT by injecting either radionuclides or radiolabelled antibodies remains experimental [53,54]. The most dreaded complication of RT is leuko-encephalopathy. This complication is frequently seen when cranial RT is combined with intrathecal (IT) methotrexate (MTX) or high dose intravenous MTX [55]. Whether the sequence of RT and chemotherapy is of influence has not been demonstrated. Characteristic for leuko-encephalopathy is progressive loss of cognitive and locomotor function that begins 3 to 8 months after RT.

Intrathecal chemotherapy

In line with the favourable experience with LM from haematologic malignancies, intraventricular chemotherapy with involved field RT has become the standard treatment for LM from solid tumours. Methotrexate is the recommended drug for intra-CSF treatment and, given as a single agent, is apparently less toxic and at least as effective as other agents or multiple agent treatment [56–58]. Other commonly used drugs for intra CSF use are cytarabine (Ara-C) and Thiotepa. These drugs are usually given as second line treatment after failure to MTX. The benefit of intrathecal Thiotepa is questionable: TEPA, an active metabolite of Thiotepa that crosses the blood-brain barrier is formed when Thiotepa is given intravenously, whereas TEPA is not formed when Thiotepa is given intrathecally (IT). Nevertheless in a randomised study intrathecal Thiotepa was as (little) effective as IT MTX [56]. The more recently developed depot Ara-C, a liposome-encapsulated sustained release formulation of Ara-C seems at least as effective as IT MTX. Depot Ara-C has the advantage of a once every 2 weeks administration, instead of twice weekly for MTX. In a randomised trial in patients with LM from solid tumours, including primary CNS tumours, time to neurologic progression was longer after IT depot Ara-C compared with IT MTX. However, after exclusion of patients with primary CNS tumours the response rates were only 12.5% for IT depot Ara-C and 17% for IT MTX [59].

Other drugs investigated for IT use such as 5fluoro-2-deoxyuridine, etoposide, mafosfamide and Interferon-α were either little effective or highly toxic [60–63]. Intrathecal use of trastuzumab was reported in a patient with LM from breast cancer, but its efficacy as single treatment is not clear [64].

The usual treatment schedule of IT MTX consists of intraventricular administration of 10 mg twice weekly until CSF cytology becomes tumour negative, followed by a less frequent administration for a couple of months as maintenance treatment. Administration of MTX by lumbar puncture is usually given at a dosage of 15 mg, however, administration by the lumbar route does not guarantee cytotoxic concentrations in the ventricles [65]. On the other hand, the recently developed depot Ara-C has been shown to achieve a constant cytotoxic concentration in the CSF, including the ventricles following lumbar administration once every two weeks [66].

The treatment results of intraventricular MTX followed by involved field RT were encouraging in several early studies, with reported response rates of 50% or more and a median survival of about 6 months for breast cancer patients and 4 month for LM from other solid tumours [10,67,68,15]. However, in nearly all later studies, the response rate was about 10–30% and the median survival 2–4 months [31,69,56,70,57,71,58,59,72–75]. In some studies not a single patient showed improvement of clinical symptoms. Obviously selection of patients played a role in the early non-controlled studies. In all studies at least one third of the patients died within a few weeks despite intensive treatment. Based on prognostic factors, patients with a very short life expectancy should be excluded from such intensive therapy. The most significant negative prognostic factors are a low performance status (Karnofsky index $\leqslant 60$), and uncontrolled systemic progressive disease. Age over 55 years, encephalopathy with confusion, cranial nerve involvement and a low CSF glucose are other negative predictive factors [2,31,6,24,76]. In patients treated with IT chemotherapy, CSF flow obstruction seems to affect outcome [48–50]. Patients with breast cancer, neurological symptoms confined to the spinal level, normal CSF protein and a CSF concentration of VEGF of < 100 pg/ml are associated with a more favourable prognosis [24,31,47,77,10].

Three randomised trials were performed comparing different IT chemotherapy regimens (i.e. MTX versus

MTX + Ara-C [57], MTX versus Thiotepa [56], MTX versus depot Ara-C [59]; see Table 1). Two of those three randomised studies included patients with non-Hodgkin lymphoma [56,57], and one study patients with primary CNS tumours [59]. Treatment results ranged from not a single improvement in one study to a response rate of 55%, and survival from 8 weeks to 15 weeks, with breast cancer patients having the best outcome. It is advised to perform a CSF flow scan using radioactively labelled indium or technetium before starting intraventricular chemotherapy [49,78]. CSF flow disturbances are reported to occur in at least 30% of patients with LM from solid tumours [48,49, 78]. Flow blockade usually, but not always, occurs at the site of macroscopic meningeal or perimeningeal tumour [48,51]. Relief of CSF blockade by local RT was associated with better outcome and less neurotoxicity [78,49]. Restoration of CSF flow by RT is successful in about half of the cases [78, 49]. Some have suggested that the application of focal RT at sites of macroscopic tumour presents a pragmatic alternative to performing an intraventricular flow scan [79]. However, whether there is a direct relationship between flow disturbances and response is unclear: a relationship could not be demonstrated between neurological response and concentration of MTX in the CSF compartments in patients with flow obstruction [51]. The poor prognosis in patients with flow obstruction due to macroscopic disease may simply reflect increased tumour burden. In addition, the better response following flow restoring RT may be more a reflection of tumour sensitivity than a direct effect of flow normalisation. Response rates defined as negative CSF cytology in the absence of neurological progression, for IT depot Ara-C and IT MTX were 12–27% and median survival 78–105 days in recent large prospective studies of patients with LM from extracranial solid tumours after exclusion of patients with flow disturbances [59,72,75].

In addition to uncertainty about the actual efficacy of IT chemotherapy in LM from solid tumours there are no data concerning the benefit of prolonged IT treatment. Retrospective studies learned that in patients with LM from breast cancer the response in the first 4–6 weeks of treatment was essential for further outcome [31,70]. Clinical status after the first 6 weeks of treatment was a better predictor of outcome than CSF cytology [31]. Patients may have tumour positive CSF cytology for many months, while they are in stable clinical condition, even without prolonged intraventricular treatment. Continuation of intraventricular therapy beyond 6 weeks did not increase survival but increased the risk of neurotoxicity [31,70]. Neurotoxicity is an important issue of the palliative treatment of LM (Table 2). Acute or subacute neurologic side effects of intrathecal chemotherapy, including aseptic meningitis, myelopathy and encephalopathy, are usually mild and transient. On occasion however, they are progressive and fatal. Aseptic meningitis of any grade was observed in 60% of patients treated with IT MTX or depot Ara-C without oral dexamethasone prophylaxis, and in about 15% of the patients with dexamethasone [59]. Slow but sustained absorption of MTX from the CSF into the plasma may lead to systemic side effects including myelosuppression and mucositis; the use of Leukovorin protects against these complications. About 20% of patients treated with intraventricular chemotherapy develop complications related to the Ommaya reservoir including infectious meningitis, intracranial haemorrhage, leakage of MTX along the reservoir, and drain dysfunction [70,31,57,71,83,81, 82]. In a randomised study the mean duration of adverse events of grade 3 or more was 18 days for patients treated with depot Ara-C and 11 days for those treated with IT MTX [89]. Late neurotoxicity consisting of leuco-encephalopathy was reported only occasionally in early studies, but more recent studies report that this serious complication with progressive ataxia and dementia may develop in as much as half of the few long survivors [31,70,47]. High peak levels of MTX, a cumulative high dose of MTX and cranial RT are associated with an increased risk of leuco-encephalopathy. In this respect CSF flow disturbances and compartmentalisation may play a role. Intrathecal Ara-C in combination with RT to the spinal cord is associated with CSF myelopathy [31,90].

Probably several factors play a role in the disputable efficacy of IT chemotherapy in patients with solid tumours, especially when compared to the efficacy in leukaemia or non-Hodgkin lymphoma. In the first place solid tumours are less sensitive to chemotherapy. Secondly in contrast to LM from leukaemia and lymphoma, LM in solid tumours is characterised by more macroscopic tumour deposits. Neurological dysfunction is mainly caused by these tumour deposits, not by free floating tumour cells in CSF space. The penetration of chemotherapeutic agents by diffusion from the CSF into these lesions is only a few cell layers and thus presumably little effective.

Systemic therapy

Experimental studies indicate that the blood-brain barrier in LM is permeable for intravenous cytostatic drugs [91]. In addition, the macroscopic tumour

Table 1
Results of intrathecal chemotherapy for LM from solid tumours in randomised trials

	Primary tumour	Results	Neurological complications	Route of IT treatment
Hitchins 1987 [57] I: IT MTX ($n=23$) II: IT MTX + IT Ara-C ($n=20$)	SCLC (30%) breast (25%) PCNS (9%) NHL (7%) ACUP (16%) other (13%)	Response: 55% (NS) MS 8 wk (NS)	Infectious meningitis (14%) Related to Ommaya: complicated insertion, fatal (5%) drain dysfunction (17%) intracranial haemorrhage (11%; 5% fatal)	41% by Ommaya 59% by lumbar puncture
Grossman 1993 [56] I: IT MTX ($n=28$) II: IT Thiotepa ($n=24$)	breast (48%) lung (23%) NHL (19%) other (10%)	Response: 0% SD 23% cytol. resp. 12% MS 15 wk (NS) (cytol. resp.: 17 wk)	Severe 36% Life threatening 18% Fatal 4%	100% by Ommaya
Glantz 1999 [59] I: IT MTX ($n=30$) II: IT depot Ara-C ($n=31$)	breast (36%) PCNS (23%) other solid tumours (41%)	Response: I: 20% II: 26% Excluding PCNS: I: 17% II: 13% MS I: 78 ds II: 105 ds	Aseptic meningitis: I: 19% II: 23% of cycles Infect. meningitis (7%)	95% by Ommaya 5% by lumbar puncture
Boogerd 2004 [80] I: IT MTX ($n=17$) (II: non-IT treatment ($n=18$))	breast 100%	Response: resp./SD 59% cytol. resp,. 35% MS 18 wk (cyt. resp: 52 wk)	Aseptic meningitis (12%) Infectious meningitis (12%) Acute encephalopathy, fatal (6%) Drain dysfunction (18%) Intracerebral haemorrhage (6%) Subdural haematoma (6%) Early delayed encephalopathy (6%) Late leuko-encephalopathy (18%)	100% by Ommaya

MS: median survival; NS: difference not significant; PCNS: primary central nervous system tumour.

Table 2
Neurologic complications of intraventricular chemotherapy

	Incidence	Risk factor	References
Related to Ommaya reservoir			
Drain dysfunction	5–10%		[24,31,47,57,68,81,82]
Infectious meningitis	5–20%		[31,80,57,68,83,81,82,84]
Subdural haematoma	0–10%		[31,80]
Cerebral haemorrhage	rare		[31]
Pericatheter Leuko-encephalopathy	rare	ICP↑	[85]
Related to chemotherapy			
Aseptic meningitis (transient)	5–>25%	Dexamethasone preventive	[24,31,47,72,82]
Seizures	very rare		[24,73]
Early encephalopathy	rare		[47,73]
Myelopathy (transient/progressive)	rare	IT MTX + IT Ara-C	
IT Ara-C + spinal RT	[31,73,82,86]		
Early delayed encephalopathy (transient)	0–20%		[55]
Optic neuropathy	very rare		[86]
Late leuko-encephalopathy (progressive)	MTX: 2–20% (=50% of long survivors) Depot Ara-C?	High dose of MTX CSF flow blockade WBRT Early delayed encephalopathy	[24,31,47,80,87,82,55,88]

ICP: intracranial pressure; IT: intrathecal.

deposits, characteristic for LM from solid tumours are well vascularised with permeable blood vessels as demonstrated by contrast enhancement on MRI scanning. These tumour deposits are better penetrated by systemically administered drugs through their permeable blood vessels than by intra-CSF chemotherapy that penetrates only a few cell layers, and efficacy will not be affected by CSF flow obstruction. Accordingly, patients with LM treated with intraventricular chemotherapy had a better neurological response and a longer survival when they also received systemic chemotherapy, though the concurrent treatment of extracranial tumour activity obviously also plays a role in this matter [31,71]. Cytotoxic CSF concentrations of MTX can be achieved after high dose intravenous administration. In a non-randomised study patients treated with high dose intravenous MTX (including 50% patients with LM from non-Hodgkin lymphoma) outcome was significantly better than in patients treated with IT MTX [92]. On the other hand, in another study of patients with LM from solid tumours not a single response was observed following high dose intravenous MTX despite cytotoxic CSF MTX levels [93]. However, because the blood-brain barrier is at least partially disrupted in LM, the intrinsic sensitivity of the tumour to the administered agent is probably more important than the CSF concentration for the likelihood a response will occur. Accordingly, durable responses were reported following standard systemic chemotherapy and even after hormonal therapy in patients with LM from solid tumours [94–96]. Cohort studies that compared IT chemotherapy plus systemic therapy and involved field RT with systemic therapy and RT alone showed no difference in neurological response and survival [31,87] (Table 3). However, treatment complications occurred significantly more often in the group treated intrathecallly. Similar results were found in the only randomised study that compared treatment with or without IT chemotherapy in patients with LM from breast cancer [80]: neurological response or stabilisation (59% in the IT group versus 67% in the non-IT group), time to neurological progression (23 weeks versus 24 weeks), median survival (18 weeks versus 30 weeks) and cause of death were not different. However, neurotoxicity occurred significantly more often in the IT group (47% versus 6%). One third of the patients treated with IT MTX, systemic therapy and involved field RT as needed achieved within a few weeks a cytological response and neurological response. Median survival of this subgroup of patients was 52 weeks.

Thus, adding IT chemotherapy to systemic therapy and involved field RT will, in general, not improve

Table 3
Results of intrathecal chemotherapy versus non-intrathecal treatment in patients with LM from solid tumours

	Study population	Results	Neurologic complications
Boogerd 1991 [31] Non-randomised non-comparative study I: IT MTX (44) II: non-IT (14)	I/II breast 100%	Response/SD I: 50% II: nr MS I: 12 wks II: 12 wks 6 months survival I: 27% II: 43% 1-year survival I: 11% II: 14%	I: IT treatment (all Ommaya): aseptic meningitis 2% infectious meningitis 11% intracranial haemorrhage 2% early delayed encephalopathy 23% myelopathy 5% late leuko-encephalopathy 25% II: none
Glantz 1998 [92] Non-randomised non-comparative study I: IT MTX (15) II: HD iv MTX (16)	I: NHL (33%) glioma (20%) NSCLC (10%) other (27%) II: NHL (50%) glioma (32%) other (18%)	Response/SD I: 47% II: 81% MS I: 2.3 mth II: 13.8 mth	I: infectious meningitis 7%
Bokstein 1998 [87] Non-randomised comparative study I: appropriate syst. ther. + RT∗ + IT MTX (54) II: appropriate syst. ther. + RT∗ (50)	I: breast 61% lung 15% other 24% II: breast 60% lung 16% other 24%	Response I: 86% II: 74% MS I: 4 mth II: 4 mth 9 mth survival I: 20% II: 18%	I: IT treatment (all Ommaya) early toxicity 31% late leuko-encephalopathy 20% II: none
Boogerd 2004 [80] Randomised clinical trial I: appropriate syst. ther. + RT∗ + IT MTX (17) II: appropriate syst. ther. + RT∗ (18)	I/II: breast 100%	Response/SD I: 59% II: 67% MS I: 18.3 wk (NS) II: 30.3 wk (NS) TTP I: 23 wk (NS) II: 24 wk (NS) 1-year survival I: 18% (NS) II: 32% (NS)	I: IT treatment (all Ommaya) see Table 2 early/late 47% II: 6% (late leuko-encephalopathy after HD i.v. MTX + WBRT) (difference I/II: $p = 0.0072$)

SD: stable disease; nr: not reported; MS: median survival; HD i.v.: high dose intravenous; RT∗: involved field radiotherapy; TTP: time to progression; NS: difference not significant.

neurological outcome or survival, but often will affect quality of life by treatment related neurotoxicity. It should be noted that most of the patients who present with LM had previously received systemic therapy, which reduces the chance of a successful systemic treatment of LM.

Symptomatic therapy

Patients with LM from solid tumours have an extraordinary poor prognosis. In the absence of favourable prognostic factors, usually only symptomatic treatment is given. Generally, treatment of the most frequently occurring symptoms such as headache, confusion and nausea and vomiting does not differ from the treatment of these symptoms when caused by other pathologies. The effects of corticosteroids on pain, neurologic deficit or irritation in patients with LM has not been thoroughly evaluated. Corticosteroids may have beneficial effects on symptoms of meningeal or nerve root irritation. The possible mechanism is the steroid induced inhibition of the inflammatory reaction caused by tumour infiltration. The dose of corticosteroids does

not have to be as high as used in treatment of brain oedema. Given the long term side effects of steroids it is advisable to discontinue the treatment at the absence of a response. For headache or vomiting due to increased intracranial pressure draining the CSF by lumbar puncture or a ventriculo-peritoneal shunt can be effective [97]. RT to the fossa posterior is sometimes effective for the palliation of excessive vomiting.

Conclusion

The treatment results of LM from solid tumours have not improved over the last decades. It now has become clear that treatment with systemic therapy and involved field radiotherapy, without intrathecal chemotherapy can be effective. In general, addition of intrathecal chemotherapy will not improve the neurological response or survival, and frequently adversely affects the quality of life by neurotoxic complications. As a consequence intensive intraventricular chemotherapy presumably will be applied less frequently. At this moment it cannot be excluded that a subgroup of patients might benefit from a combination of systemic therapy, IT chemotherapy and local RT. Moreover, IT chemotherapy can still be indicated in patients for whom systemic treatment is not an option. Duration of IT treatment beyond 6 weeks is probably not meaningful and increases the risk of toxicity. In view of possible Ommaya reservoir related complications lumbar IT administration of depot Ara-C might be preferred above intraventricular MTX.

Conflict of interest statement

None declared.

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