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short review

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Summary Leptomeningeal metastases from solid tumours are increasingly being diagnosed and require a careful assessment by an interdisciplinary neuro-oncological tumour board for adequate diagnosis, therapy planning and optimal care of the affected patients.

Keywords Carcinomatous meningitis · Leptomeningeal carcinomatosis · Leptomeningeal metastases · Neoplastic meningitis · Intrathecal therapy

An increasing number of patients with metastatic cancer are developing leptomeningeal dissemination due to better therapies and longer survival. In a brief review, we will focus on leptomeningeal disease arising from solid tumours and inform about current management and future directions.

Leptomeningeal metastases (LM) are defined by the presence of metastatic tumour cells within the leptomeninges and the subarachnoid space. Overall, leptomeningeal involvement is diagnosed in about 10–15% of patients with metastatic solid tumours, with an increasing tendency, due to longer survival of patients with the associated tumours and better access to modern imaging. Three tumour entities are particularly prone to spread to the meninges: (1) breast cancer [1], (2) lung cancer, notably molecular driven subtypes of NSCLC and SCLC, and, (3) melanoma. The highest incidence of LM appears to be in melanoma (23%) and lung cancer (9–25%) then followed by breast cancer (5%). Considering the high incidence of breast cancer worldwide, in absolute numbers it constitutes the most common aetiology of LM. Rarely, leptomeningeal metastases are a first tumour manifestation. Concurrent systemic disease progression is seen in up to 60–70% of patients. Brain metastases are noted in about 40%, half of them progressing at leptomeningeal metastases diagnosis, new brain metastases have been reported in 20% [2, 3].

Prognosis of leptomeningeal tumour manifestation is generally poor, with a median survival limited to a few months in most patient cohorts, with the exception of molecularly altered tumours which are accessible to targeted drugs and a longer disease control may therefore be expected.

A literature search on this particular tumour manifestation provides information on the following terms: “meningeosis carcinomatosa”, “carcinomatous meningitis”, “neoplastic meningitis”, “leptomeningeal carcinomatosis” and “leptomeningeal metastases”. Hereafter, the term leptomeningeal metastases will be used, abbreviated as “LM”.

Pathophysiology

The leptomeninges and the subarachnoid space are reached by the haematogenous route through the “blood–leptomeningeal barrier (BLB)”, a vascular structure, which is semipermeable at least for tumour and immune cells. Cancer cells that reach the brain microvasculature may also cross the “blood–CSF barrier” via the choroid plexus to enter the ventricles and the leptomeningeal space. Furthermore, direct tumour cell invasion can occur from infiltrating brain metastases. Finally, tumour cells can migrate via

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vessels of the skull, from vertebral bodies and via perineural and perivascular routes. Rather rarely, leptomeninges are colonized iatrogenically, i.e. after brain metastasis resection [4]. Various CNS barriers hinder—at least partially—therapeutic drug concentrations in the brain after systemic administration [5].

Diagnostics

Symptoms may initially be discrete, unspecific and variable, and may involve multiple localizations i.e. any part of the neuraxis. Typical symptoms include headache, nausea and vomiting, mental changes, dizziness and drowsiness, gait difficulties, cranial nerve palsies with diplopia, visual disturbances, hearing loss, sensorimotor deficits of the extremities, cauda equine syndrome, and radicular neck and back pain. Contrast-enhanced magnetic resonance imaging (MRI) is the first mandatory diagnostic procedure. The whole cerebrospinal neuraxis should always be assessed to determine the extent of the disease. MRI findings include sulcal and foliar enhancements, linear ependymal and cranial nerve root enhancement but also leptomeningeal enhancing nodules. Of note, about 20–30% of patients with LM have a normal or false-negative MRI. After exclusion of a hydrocephalus, diagnosis of LM is confirmed by malignant cells in the CSF. It should be noted that the first cerebrospinal fluid sample obtained is only diagnostic in about 50% and should be repeated if deemed necessary [3]. For quality reasons, it is important to ensure a sufficient amount of cerebrospinal fluid (5–10 ml) and rapid processing of the material (within one hour). Tumour markers, such as CEA or CA 125, when present in the primary tumour, can be determined in the CSF for diagnostic and follow-up purposes. CSF tumour markers reflect intrathecal production; the concentration is higher than in the serum. They may also support the diagnosis in case of a lack of tumour cells in the CSF; however their role in clinical practice, is limited [6]. Circulating tumour DNA (ctDNA) in the CSF is a complementary tool for diagnosis and characterization of LM. ctDNA may detect actionable genomic alterations and resistance mutations not present in metastases in the periphery.

In the absence of tumour cells in the CSF, neurological symptoms and typical craniospinal MR findings strongly support the diagnosis of cancer in a patient.

Leptomeningeal growth pattern and therapeutic consequences

A distinction is made between nodular tumour growth, adherent to the meninges, linear spread and freely floating tumour cells or a combination of these manifestations (Fig. 1).

Therapeutic consequences result from these different growth patterns, as assessed by imaging and

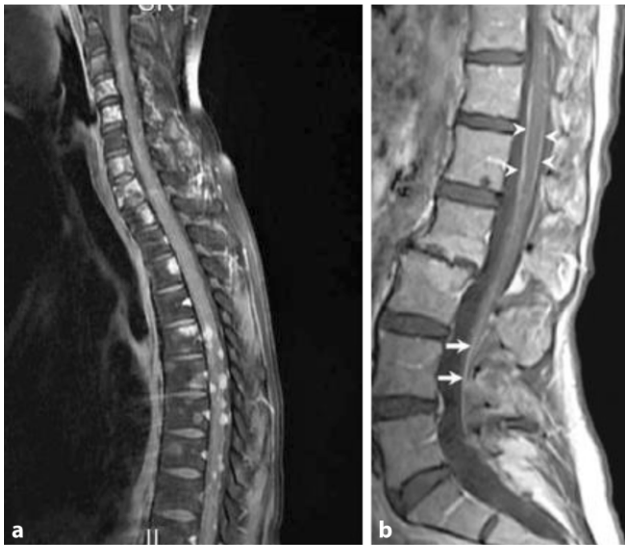

Fig. 1 Nodular (**a**) and linear (**b**) leptomeningeal tumour growth

CSF cytology. In case of extensive nodular and symptomatic manifestation, local radiotherapy (RT) is recommended, whereas 1–2 mm layers or freely circulating tumour cells are probably more accessible to intrathecal (i.th.) and systemic therapy. We would rather not recommend i.th. therapy for nodular disease without a positive CSF cytology on repeated sampling through lumbar puncture. RT may also be an option for the treatment of CSF flow blocks.

Without any treatment, leptomeningeal spread is fatal within a few weeks. With conventional systemic therapy, median survival is about 3–6 months. Targeted therapies can achieve much longer lasting tumour control, especially in HER-2 positive, EGFRmut and ALK driven tumours.

Local therapeutic options

Surgical intervention for leptomeningeal disease is rarely needed, except for the insertion of an intraventricular reservoir for drug administration or for a ventriculoperitoneal shunt in case of intracranial hypertension. Hereby, blockage of the shunt due to tumour cell clusters is a dreaded complication. The overall complication rate of ventriculoperitoneal shunts is estimated to be between 9 and 15% [7]. Hydrocephalus can also be corrected by third ventriculostomy, using no implants and having little risk of blockage. The decision on how to manage LM-associated hydrocephalus is complex and requires close collaboration amongst physicians, patients, and/or proxies with a focus on patient's quality-of-life [8].

Focal radiotherapy is indicated in symptomatic nodular lesions, to correct cerebrospinal fluid circulation, for rapid treatment of tumoural cranial nerve affections, cauda equina symptoms or for the simultaneous treatment of brain metastases. Whole brain

radiotherapy (WBRT) covers a large part of the cerebrospinal fluid space and may be indicated in the absence of other options. However, WBRT does not confer a survival advantage, and comes along with serious neurocognitive disorders. Irradiation of the whole cerebrospinal axis is not recommended due to its toxicity.

Intrathecal therapies

Intrathecal (i.th.) administration of suitable drugs is recommended under the condition of floating tumour cells (CSF cytology) and/or linear tumour spread (up to 1–2 mm thickness) [3]. Advantageous for successful intrathecal treatment is, as for any therapeutic intervention, good tumour control outside of the CNS and an adequate performance status without severe neurological deficits. A more favourable drug distribution can be achieved by a reservoir with direct access to the ventricles (e.g. Ommaya reservoir) compared to repetitive lumbar punctures. The revision rate of such a reservoir in trained hands is 7–8%, while the infection rate is reported to be 5–10% [9]. In case of suspected obstruction, CSF flow studies may be performed to evaluate the patency of the CSF circulation before moving to intrathecal therapy.

There are no randomized studies (RCT) to compare intrathecal therapy versus "best supportive care" for solid tumours. However, there are randomized data on systemic therapy with and without additional intrathecal therapy in breast cancer. A recent study with i.th. liposomal cytarabine (drug currently not available) showed prolonged progression-free survival (PFS) for leptomeningeal involvement and a trend towards an improved survival [10]. An older RCT, with some methodological weaknesses, did not report such an advantage for the combination of systemic and intrathecal chemotherapy. Furthermore, increased neurotoxicity with i.th MTX was observed and an unexpected high complication rate with the ventricular devices occurred in this study [11].

Of note, the old drugs, which we have been using intrathecally for more than 40 years, are not well suited to achieve good tumour control in most of the affected cancers. MTX, thiotepa, cytarabine, gemcitabine, topotecan and etoposide are not the preferred drugs for most common tumours that metastasize to the leptomeninges and all of them have a short half-life (4–8 h), which is why these drugs have to be administered two times per week, at least initially. Other disadvantages are local and sometimes irreversible toxicities (e.g. arachnoiditis, myelopathy, progressive leukoencephalopathy).

In recent years, some monoclonal antibodies have been successfully administered intrathecally and preliminary experience has been gathered in phase I studies, small case series and individual observations. Activity of intrathecally administered monoclonal antibodies in the three compartments "cerebrospinal fluid", "brain parenchyma" and "blood" is most interesting, partly unexpected and not yet fully understood. Intrathecally administered antibodies may work partly through antibody-dependent cellular toxicity (ADCC) or complement-dependent cytotoxicity (CDC) [12].

For intraventricularly administered rituximab, a pharmacokinetic model was developed that suggests a certain penetration of antibodies into the brain parenchyma. Furthermore, elimination of the antibodies from the CSF into the serum has been demonstrated by pharmacokinetic studies. High, i.e. therapeutic, serum levels have been measured after intrathecal trastuzumab and rituximab without systemic treatment [12–14]. A pooled analysis of 58 patients with HER-2 positive breast cancer confirmed safety and efficacy of i.th. trastuzumab [15]. A first phase I dose escalation study with 16 patients recommends 150 mg i.th. trastuzumab weekly [16]. Our own observations with CSF and serum trough levels could show that even 150 mg every 3 weeks is effective to control leptomeningeal disease, in one patient lasting for more than 4 years [17]. Time from the first i.th. trastuzumab until improvement of neurological symptoms, and lack of detectable tumour cells in the CSF was 3, 2, and 1 month, respectively, in 3 subsequent patients. Disappearance of MR contrast-uptake was observed after 4 and 3 months, respectively. All 3 patients had previously received WBRT. Trastuzumab CSF concentrations (trough level) >0.1 mg/L allowed leptomeningeal tumour control over time in our small series. Remarkably, trastuzumab serum concentrations after 3-weekly intrathecal application alone reached 30 mg/L, corresponding to therapeutic serum levels [13]. The elimination process of trastuzumab and other antibodies from the CSF into the blood and the best combination with systemic treatment remains to be investigated. Moreover, the question regarding duration of i.th. antibodies beyond clinical improvement is still unresolved.

No acute neurotoxicity has been described for i.th. monoclonal antibodies such as rituximab, trastuzumab, bevacizumab, nivolumab or panitumumab; however, long-term toxicity over several years cannot be excluded. Provided that intrathecally administered immune checkpoint inhibitors may show efficacy in the near future in controlling leptomeningeal disease of immune-responsive tumours such as melanoma, NSCLC, SCLC, renal cell and triple-negative breast cancer, the drug reservoir "CSF" could become an interesting therapeutic niche. Further pharmacokinetic studies will have to show whether intrathecal antibody therapy alone may substitute for systemic administration.

Systemic therapies

Few specific data are available for leptomeningeal disease and systemic therapy; most have been extrapolated from patients with brain metastases or advanced disease.

Classical chemotherapy has been used for leptomeningeal disease and some have proven to be active in sensitive tumours, among others, 5-fluorouracil, capecitabine, pemetrexed cisplatin, carboplatin, vinorelbine, gemcitabine, high-dose methotrexate (≥3 g/m^2), thiotepa, high-dose cytarabine, etoposide, eribulin.

The **anti-HER-2 monoclonal antibodies** trastuzumab and pertuzumab have in general modest activity when administered as monotherapy in metastatic HER-2-positive disease and they do not cross an intact blood–brain barrier. Concomitant chemotherapy administration is needed for optimal extracranial activity. In addition, there is statistically and clinically significant improved response and time to progression for the continuation of trastuzumab beyond progression in the management of women with HER-2-positive advanced breast cancer [18] and it has been suggested that an improvement of systemic disease control delays the onset of brain metastasis (BM), as has been demonstrated in the CLEOPATRA trial [19].

Similar observations are reported for the anti-HER-2 **antibody-drug conjugate ado-trastuzumab emtansine (T-DM1)** where the chemotherapy backbone has been directly linked to the antibody, allowing targeted tumour delivery of an otherwise toxic compound, DM1, a potent microtubule polymerization inhibitor.

T-DM1 activity in central nervous system metastasis was assessed in a retrospective, exploratory analysis of the EMILIA randomized phase III trial, comparing safety and efficacy of T-DM1 with standard of care, capecitabine and lapatinib. In participants who had been previously treated with trastuzumab and a taxane, the analysis suggested that T-DM1 may confer a survival advantage over capecitabine and lapatinib in patients with treated, asymptomatic brain metastases [20].

A post hoc exploratory subgroup analysis of the KAMILLA trial in 398 anti-HER-2 pretreated patients with asymptomatic BM represents the largest cohort treated with T-DM1. A clinical significant benefit was observed in patients with and without prior radiotherapy [21]. Combination strategies with immunotherapy are worth exploring, as T-DM1 treatment seems effective in increasing the presence of TILs [22].

A non-randomized phase II study with the CNS-penetrant **CDK4 inhibitor** abemaciclib for hormone receptor-positive breast cancer patients with brain and leptomeningeal metastases did not meet its primary endpoint (intracranial response rate, iORR), but an intracranial clinical benefit rate (iCBR) was described for the cohort with highly pretreated hormone receptor-positive, HER-2-negative breast cancer patients. iCBR in the study was defined as CR, PR or SD ≥6 months. Fourteen out of 55 patients of cohort A (hormone-receptor-positive, HER-2-negative) had an iPR or iSD >6 months, resulting in an iCBR of 24.1%. [23].

Activity of anti-hormonal drugs, such as tamoxifen or aromatase inhibitors, has been reported in the brain and in the leptomeninges and could potentially be considered in responsive tumours [24].

Next generation targeted **tyrosine kinase inhibitors** (TKI) with small molecular weight (400–500 D), low or lacking dependence on efflux transporters (e.g. P-glycoprotein, Pgp)—not a sole criterion though—have been reported to have clinically meaningful activity in the CNS and may even have preventive potential on the formation of new LM or brain metastases in tumours with corresponding actionable targets.

Examples are osimertinib for *EGFR*mut, alectinib for ALK- and RET-, lorlatinib for ALK—and ROS 1 and brigatinib for EGFR-, ALK- and ROS1-altered NSCLC, but also vemurafenib or dabrafenib with and without MEK-inhibitors for *BRAFV600E*mut tumours (Table 1). They have all shown to result in impressive and often durable intracranial responses [25]. Exem-

Table 1 Selected molecular targeted agents for LM from NSCLC (adapted from [25])

Drug	Target	MW	Substrate for efflux transport	CNS penetration (CSF/plasma or CSF/blood)
Erlotinib	EGFR	393	Yes	2.8% to 3.3%
Gefitinib	EGFR	447	Yes	1.13%
Afatinib	EGFR	486	Yes	1.65%
Osimertinib	EGFR (T790M)	500	Yes	2.5% to 16%
Zorifertinib	EGFR	460	No	100%
Crizotinib	ALK, MET, ROS1	450	Yes	0.26%
Ceritinib	ALK, ROS1	558	Yes	15%
Alectinib	ALK, RET	483	No	63% to 94%
Brigatinib	ALK, ROS1, EGFR	529	Yes	no data
Lorlatinib	ALK, ROS1	406	Yes, but low	31% to 96%
Vemurafenib	BRAF	490	Yes	0.98%

LM leptomeningeal metastases, *NSCLC* non-small cell lung cancer, *MW* molecular weight

plary, in ALK-TKI refractory NSCLC patients with LM, the intracranial ORR, intracranial disease control rate, median duration of treatment and median PFS were 45% and 91%, 5.3 months, and 9.3 months respectively [26]. A higher incidence of LM was observed in NSCLC patients harbouring *EGFR* mutations after an effective EGFR TKI treatment. In particular, mutation L858R potentially predicts a higher risk of LM compared with deletion of exon 19. These results highlight the importance of determining the current mutational status, preferentially from liquid biopsies of the CSF [25, 27].

Lapatinib is effective to a lesser extent for HER-2-positive tumours due to its dependence on the Pgp. Tucatinib, a highly selective TKI against HER-2, has reported activity in 75 untreated patients with HER-2-positive brain metastases in combination with trastuzumab and capecitabine; intracranial ORR of 47.3% could be reached in the HER2CLIMB trial [28].

While the current evidence on the activity of TKIs comes from case series and retrospective studies with LM, prospectively collected data are becoming available in rapid succession.

Immune checkpoint inhibitors (IO) have been shown to be effective in the brain by exerting activity on BM and LM indirectly by T cell responses [29, 30] and thus might even have prophylactic potential, as has been suggested by a lower incidence of new BM with durvalumab in NSCLC [31]. Combining IO with RT might further augment the efficacy (Table 2).

Concluding remarks

For leptomeningeal disease intrathecal therapy seems particularly useful when targeted drugs with a long half-life are available, e.g. trastuzumab. Systemic therapies with the ability to overcome brain barriers are only effective if tumour cells are sensitive. A common feature of all systemically administered drugs is a heterogeneous uptake into the leptomeninges, which may explain, at least in part, their limited efficacy. Some patients may benefit from systemic treatment beyond progression in the CNS if they are offered local treatment for their intracranial disease. For all these considerations, the neurological and general condition and the patient's wish must be taken into account in a difficult-to-treat disease manifestation with still poor outcome.

Table 2 Drugs most commonly used for leptomeningeal disease from solid tumours

Intrathecal drugs	
Methotrexate, 10–15 mg	Initially 2 ×/week
Thiotepa, 10 mg	Initially 2 ×/week
Trastuzumab, 150 mg	Weekly to three weekly
Systemic drugs	
Next generation TKI	According to target, taking into account resistance mechanisms
Chemotherapeutic drugs	According to sensitivity or resistance of the tumour
HER-2 directed therapies	T-DM1 and next generation TKIs
Anti-hormone therapies	Tamoxifen, aromatase inhibitors
CDK 4 inhibitors	Abemaciclib
Immunotherapies	PD-L1 antibodies

Future directions

The CSF space is a challenging niche for metastatic tumour cells. Recent research focused on the biochemical composition of the CSF in the setting of leptomeningeal metastases. Mechanisms of cell survival and distinct gene expression signatures were discovered. Some appear to act via a high-affinity iron transport system to maintain iron-dependent cellular survival functions and the suppression of local macrophage activation by iron deprivation. Whether this iron-capturing system also confers increased survival of circulating tumour cells requires further investigations [32].

Cell-free circulating tumour DNA (ctDNA) in the CSF holds useful information regarding diagnosis to better characterize LM, detect actionable genomic alterations and monitor responses to therapy [33].

Take Home Message

- Leptomeningeal metastases should be treated according to the clinical, MRI and cytological presentation, taking into consideration the general and neurological status, molecular characteristics, other metastatic sites and prior treatments.
- Promising approaches are under development and trials should be conducted specifically for this patient population.

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