Interdisciplinary management of central nervous system metastasis and neoplastic meningitis: recent developments and future perspectives

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ABSTRACT

The incidence of metastatic disease in the central nervous system (CNS) is rising. According to current estimates, up to a third of adult cancer patients will suffer from CNS metastasis. Clinical evidence-based data from prospective randomized trials are rare, however, because CNS metastasis patients were often excluded from clinical trial participation. The management of CNS metastasis patients is therefore rather ill-defined and an interdisciplinary challenge. Recent basic and translational science data have begun contributing to a more profound understanding of the molecular mechanisms leading to invasion of tumor cells into the CNS. This report reviews advances, challenges, and perspectives in this field.

Key words: Brain tumor; central nervous system metastases; interdisciplinary management

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INTRODUCTION

Invasion of tumor cells from primary tumors of the central nervous system (CNS) to organs outside the CNS is a highly rare event. In contrast, invasion of tumor cells arising outside the CNS to brain, spinal cord, or cerebrospinal fluid (CSF) occurs frequently, leading to CNS tumor growth and neoplastic meningitis. Moreover, in approximately every tenth patient, the diagnosis of brain metastasis is the first sign of the cancer disease.\[1\]

CNS metastases are the most common intra-axial malignancies, accounting for more than 50% of all brain tumors,\[2\] occurring in 20-40% of patients with cancer, and leading to symptoms during lifetime in about 60-75%.\[3\] Autopsy series identified CNS metastases in 15-41% of patients with known primary cancers at the time of death.\[4,5\] Most metastatic manifestations affect the brain parenchyma; 80% are found supratentorially and 20% infratentorially (15% cerebellum, 5% in the brain stem), with the spinal cord most infrequently involved. The incidence of single vs. multiple sites of CNS metastasis is approximately equal.\[6,7\] In about 4-15% of patients with CNS disease, CSF is involved.\[8\] Lung cancer, breast cancer, and melanoma are the primary malignancies that contribute to 80% of brain metastases.\[7,11,12\] Moreover, there is a high incidence of asymptomatic CNS metastases, so it is hard to estimate their true prevalence. Current studies estimate that approximately a third of patients with cancer eventually develop brain metastases.\[10\]

Several reasons may explain the increase in incidence of brain metastases over the past decades: Certainly, the widespread use and improvements in new imaging technologies facilitates the detection of metastatic lesions. For example, magnetic resonance imaging (MRI) of the neuraxis is currently used for the examination of approximately 60-70% of patients with cancer; 20 years ago, it was used in 2% of cancer patients.\[13\] The global increase in cancer prevalence is another contributing factor, especially the increase in cancers that have a tendency to invade the CNS, such as lung cancer. Moreover, the introduction of targeted therapies that have limited bioavailability in the CNS might also have resulted in an increase of CNS metastases (e.g. the treatment of human epidermal growth factor receptor protein 2(HER2)-positive breast cancer with trastuzumab, a compound with limited penetration from the blood to the CSF).\[14,15\]

Neoplastic meningitis (also referred to as meningoeis neoplastica or, based on the underlying tumor, as meningoeis carinomatosa, gliomatosa, or lymphomatosa) is a spread of tumor cells into the subarachnoid space. It is found in approximately 5-10% of all patients with malignant tumors and is a condition frequently diagnosed in late stage cancer.\[16\] The most common associated primary tumors are lung cancer, breast cancer, melanoma and lymphoma and leukemia.\[17\]

Patients with CNS metastases present with rather unspecific clinical symptoms. Headaches (40-50%), focal neurological deficits (30-40%), and seizures (15-20%) are the most common presenting symptoms. In leptomeningeal disease many symptoms are caused by an increased intracranial pressure mainly due to hydrocephalus, which leads to nausea and vomiting, neck and back pain, and confusion.\[3\]

MOLECULAR MECHANISMS OF CENTRAL NERVOUS SYSTEM METASTASIS FORMATION AND MAINTENANCE

Cancers that metastasize to the CNS need to undergo multiple steps, including detachment from the primary site, invasion, intravasation into the bloodstream, extravasation, survival, and proliferation. Even with different primary tumor origins, invasion and proliferation into the CNS appears to be associated with similar molecular programs and is highly supported and maintained by the tumor-associated brain microenvironment.\[18\]

First, the growth of metastatic brain tumors is critically dependent on angiogenesis,\[19\] so therapies targeting this process might be important in the prevention or management of brain metastases. In a mouse model of brain metastases [HER2-amplified breast cancer cells in an orthotopic xenografting of human BT-474 cells], extracranial disease was successfully controlled using the HER2 inhibitors trastuzumab or lapatinib, but tumor control with monotherapy in the brain failed. By adding anti-VEGFR2 antibodies, however, tumor growth in the brain was better controlled, leading to improved survival, especially with a combination of lapatinib, trastuzumab, and anti-VEGFR2 antibody treatment.\[20\]

Second, astrocytes are intimately involved in maintaining normal homeostasis of the brain microenvironment, accomplished through transport of nutrients to the neurons and facilitation of neural signal transduction. In fact, activated astrocytes induced upregulation of survival genes. These mechanisms usually protect injured neurons from apoptosis, but can be abused by tumor cells (e.g. for protection from cytotoxic effects of chemotherapeutic agents).\[21,22\] A very interesting study on the impact of astrocyte-derived reshaping of the brain microenvironment was recently published by Zhang and colleagues: Mouse tumor cells lost PTEN expression only after dissemination to the brain, but not to other organs, and PTEN levels in PTEN-loss brain metastatic tumor cells were again rescued after leaving the brain microenvironment. This brain microenvironment-dependent plasticity of PTEN expression is epigenetically regulated by astrocyte-derived exosomes mediating an intercellular transfer of PTEN-targeting microRNAs to metastatic tumor cells. As a
result of this adaptive PTEN loss, brain metastatic tumor cells released more chemokine CC chemokine ligand 2, leading to recruitment of IBA1-expressing myeloid cells and further enhancement of the growth and maintenance of brain metastases.[33] Infiltrating inflammatory host cells, including tumor-infiltrating lymphocytes or myeloid cells, are a third key component shaping the tumor microenvironment and correlating with patients’ survival times in several extracranial malignancies.[24] These cells significantly change their functional characteristics under the influence of high-grade glioma,[23] indicating that they might also play a role for supporting CNS metastatic growth. Clinicopathological correlations of associated lymphocytic infiltrates indicate a beneficial outcome for CNS immune response.[26] Two functional phenotypes of tumor-associated macrophages have been proposed: the M1 and the M2 phenotype. While M1 is characterized by tumor-suppressive functions, the M2 may have more tumor-promoting functions, including suppression of immune responses and promotion of adaptive immune response and migration/invasion.[25] However, recent studies suggest that this dichotomy does not completely reflect the situation in brain tumors.[27]

In recent years, high-throughput technologies have evolved significantly. Thus, molecular tumor profiling (e.g. by Next-generation sequencing, panel sequencing) for identifying molecular targets is in principle feasible in the short term. Data on the molecular characteristics of CNS metastases have only recently been acquired. This might be due to the fact that CNS metastatic tissues are only available from patients who are eligible for neurosurgical resection. Because craniotomies are not indicated in all patients with CNS metastases (see below), a systematic analysis of the molecular differences between CNS metastases and matched primary tumors or between CNS metastases and extracranial metastases remains challenging. Molecular profiling of matched CNS and extracranial metastases in smaller series of melanoma patients showed that CNS metastases distinguished themselves through specific molecular differences in the activation of the PI3K/mTOR/ Akt or HER2 or kirsten rat sarcoma (KRAS) pathway.[28-31] These studies highlight, for example, the potential of adding PI3K inhibitors or mTOR inhibitors as adjunct targeted therapy in the treatment of CNS metastases.

**TREATMENT STRATEGIES NEED A PROFOUND INTERDISCIPLINARY DIAGNOSTIC WORKUP**

In addition to the staging of extracranial disease, a thorough neurological workup including neurological examination, neurocognitive assessments, neuroimaging, and a spinal tap is in principle indicated in all patients with established malignant disease and suspected brain metastases. Depending on clinical symptoms and neuroradiological features, one single spinal tap or up to three spinal taps can be considered. If, for example, clinical symptoms strongly suggest an underlying meningioma, a single lumbar puncture might not be enough to detect atypical cells in the CSF, so serial lumbar punctures might be necessary. Diagnostic workup of the CSF includes analyses of opening pressure, protein, glucose, and lactate levels as well as cytology and immunocytology.

Standard MRI exams include T1-weighted images with or without contrast enhancement, T2-weighted imaging, and FLAIR sequences. Differential diagnosis of brain metastases includes malignant gliomas and lymphomas or nonneoplastic conditions, such as abscess, infections, demyelinating diseases, and vascular lesions. Recently, the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) working group has proposed criteria for a harmonization of the assessment of CNS metastases.[32] This might contribute to a standardization of techniques and assessment tools, particularly important in the era of targeted compounds. It is not yet entirely clear to what extent and how novel targeted therapies (e.g. immunotherapies and kinase inhibitors) will alter imaging characteristics. The recently published recommendations of the RANO-BM working group provide a guideline to differentiate imaging alterations during immunotherapies in brain tumors.[33] Innovative and advanced neuroimaging techniques will certainly gain even more importance. Examples include the addition of diffusion-weighted MRI (DW-MRI), perfusion MRI, proton magnetic resonance spectroscopy (MRS), and various amino acid tracers in positron emission tomography (PET). These techniques might be especially relevant to meet the challenges of disease monitoring (e.g. the discrimination of radiation necrosis from recurrent tumor might be challenging on MRI since both conditions present with contrast enhancement on T1-weighted MR images, and the pattern of abnormal enhancement closely mimics that of a recurrent brain metastasis).[34] In fact, small studies with perfusion MRI using CBV analysis showed the potential to differentiate between radiation necrosis and tumor recurrence with good sensitivity and specificity.[35] Nuclear medicine techniques might contribute to answering this critical question. While an fludeoxyglucose (FDG) tracer was not sensitive enough to differentiate vital brain metastases from unspecific non-tumor changes related to therapy,[36] the amino-acid PET tracer ¹¹C-methionine showed higher tumor-to-lesion uptake ratios in patients with recurrent metastases/glioma after radiation treatment than in patients with radiation necrosis.[37] Furthermore, the combination of two amino acid tracers (FET and MET) identified treatment-related changes with high sensitivity and specificity.[38]

The blood-brain-barrier is often mentioned as a challenge for diagnosis and therapy. In a very interesting preclinical study using mouse models of small metastatic breast
tumors, infusions of recombinant human tumor necrosis factor induced selective permeabilization of the blood-brain barrier to imaging tracers at sites of brain metastases. This method enabled the detection of smaller tumors that had been invisible using standard imaging techniques. Notably, this strategy even increased the delivery of radiolabeled trastuzumab to these metastatic lesions, demonstrating the translational potential of similar approaches for theranostics.

THE ESTIMATION OF PROGNOSIS IS IMPORTANT FOR CLINICAL MANAGEMENT

The most widely established risk stratification scores are the Recursive Portioning Analysis (RPA), the Graded Prognostic Assessment (GPA), and Diagnosis Specific Graded Prognostic Assessment (DS-GPA) [Table 1].

Definitely, the presence of neoplastic meningitis in patients with solid tumors indicates a poor prognosis. Negative prognostic factors associated with leptomeningeal tumor cell dissemination are low Karnofsky performance status (KPS), increased age, uncontrolled intracranial pressure, low glucose levels, and high protein levels.

RPA divides patients into three categories based on KPS, age, and primary tumor control, with patients in group I having a better prognosis than patients in group III. The GPA evaluates the prognosis of patients with brain metastases based on the primary tumor diagnosis. Histology carries prognostic significance, along with other subcategories (e.g., age and extracranial disease in lung cancer patients, or number of metastases in melanoma patients). Tumor subtype based on HER2/ER/PR status and age is prognostic for breast cancer and is expanded upon with a specific breast-GPA, currently in use in clinical trials. Other prognostic scores were defined and are summarized in Table 1. In large retrospective studies of melanoma patients with brain metastases, poor prognostic factors associated with worse survival were: > 3 parenchymal lesions, leptomeningeal disease, brain lesions developing concurrently with extracranial disease or while on systemic therapy for extracranial disease, poor performance status (KPS < 70%), elevated pretreatment LDH levels, and RPA class III.

Table 1: Prognostic scores

<table>
<thead>
<tr>
<th>Recursive partitioning analysis</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
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<tbody>
<tr>
<td>Age &lt; 65</td>
<td>KPS &gt; 70%</td>
<td>Stable primary tumor</td>
<td>All patients not in Class I or class III</td>
</tr>
<tr>
<td>KPS &gt; 70%</td>
<td>No extracranial metastases</td>
<td>KPS &lt; 70%</td>
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</table>

Basic score for brain metastases

<table>
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<tr>
<th>Score</th>
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<tbody>
<tr>
<td>KPS 50-70%</td>
<td>80-100%</td>
<td></td>
</tr>
<tr>
<td>Control of primary tumor</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Extracranial metastases</td>
<td>No</td>
<td></td>
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</tbody>
</table>

Score index for radiosurgery

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<td>Age (years)</td>
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<td>51-59</td>
<td>&lt; 50</td>
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<tr>
<td>KPS &lt; 50%</td>
<td>60-70%</td>
<td>80-100%</td>
<td></td>
</tr>
<tr>
<td>Systemic disease</td>
<td>Progressive</td>
<td>Stable</td>
<td></td>
</tr>
<tr>
<td>Number of lesions</td>
<td>&gt; 3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Volume of largest target lesion</td>
<td>&gt; 13 mL</td>
<td>5-13 mL</td>
<td>&lt; 5 mL</td>
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Graded prognostic assessment

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<tr>
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<td>50-59</td>
<td>&lt; 50</td>
<td></td>
</tr>
<tr>
<td>KPS &lt; 70%</td>
<td>70-80%</td>
<td>90-100%</td>
<td></td>
</tr>
<tr>
<td>CNS metastases (no.)</td>
<td>&gt; 3</td>
<td>2-3</td>
<td></td>
</tr>
<tr>
<td>Extracranial metastases</td>
<td>Present</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis-specific graded prognostic assessment

i) NSCLC/SCLC

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<th>1.0</th>
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<tr>
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<td>50-60</td>
<td>&lt; 50</td>
<td></td>
</tr>
<tr>
<td>KPS &lt; 70%</td>
<td>70-80%</td>
<td>90-100%</td>
<td></td>
</tr>
<tr>
<td>Extracranial metastases</td>
<td>Present</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>CNS metastases (no.)</td>
<td>&gt; 3</td>
<td>2-3</td>
<td></td>
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</table>

ii) Melanoma/RCC

<table>
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<th>Score</th>
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<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS &lt; 70%</td>
<td>70-80%</td>
<td>90-100%</td>
<td></td>
</tr>
<tr>
<td>CNS metastases (no.)</td>
<td>&gt; 3</td>
<td>2-3</td>
<td></td>
</tr>
</tbody>
</table>

iii) Breast/G1 cancer

<table>
<thead>
<tr>
<th>Score</th>
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<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS &lt; 70%</td>
<td>70%</td>
<td>80%</td>
<td>90%</td>
<td>100%</td>
</tr>
</tbody>
</table>

CNS: central nervous system; KPS: karnofsky performance status; NSCLC: non small-cell lung cancer
The prognostic indices certainly play an important role in assessing the risk/benefit ratio and providing realistic advice and expectations to patients. For example, patients with poor prognosis can be offered supportive care, and those with good prognosis can be offered multimodality treatment. The prognostic scores might play a vital role in designing clinical trials as well.

Information about variables on neuroimaging, in addition to the pure number of brain metastases, might be valuable extensions to currently established prognostic scores. Spanberger and colleagues found a significant correlation between a small brain edema with an invasive tumor growth pattern, a low neo-angiogenic activity, and a low expression of HIF1α. These findings were associated with a shorter overall survival.[50] Further, high DW-MRI hyperintensity correlated significantly with a high amount of interstitial reticulin deposition, and this was again associated with lower survival.[51] Similarly, pre-operative DW-MRI characteristics of cerebral metastases and their peritumoral region in 76 patients were related to patient outcome.[52]

**THERAPEUTIC APPROACHES TO CENTRAL NERVOUS SYSTEM METASTASIS**

CNS metastases are, of course, a heterogeneous group with varied response to treatment and survival. Conventional treatment options usually include a combination of steroids, surgery, and radiation. Cytotoxic chemotherapy has had a limited role in the treatment of brain metastases, probably because CNS metastases often arise from heavily pretreated primary tumors and may thus have already acquired resistance to chemotherapeutics. In addition, the impaired blood-brain barrier penetration of some agents may thus have already acquired resistance to chemotherapeutics. In addition, the impaired blood-brain barrier penetration of some agents might further reduce their bioavailability in the CNS. Therapeutic decisions mainly depend on several factors related to patient clinical status (neurological deficit, neurocognitive deficit, general condition, comorbidities, etc.), primary disease status, extracranial metastatic disease, and CNS tumor characteristics (number, radiological aspect, size, and location).[40] Median overall survival times after occurrence of CNS metastases might be predicted by biomarkers as shown for LDH elevation in melanoma CNS metastases.[58] All relevant clinical factors need to be taken into account to identify the best therapeutic strategy among the available therapeutic options. We outline the currently available local and systemic therapeutic options in the following paragraphs.

**LOCAL THERAPEUTIC STRATEGIES: NEUROSURGICAL INTERVENTION AND RADIATION THERAPY**

Neurosurgical intervention and radiation therapy are currently the main modalities in the therapy of symptomatic CNS metastases. New surgical modalities have expanded the indication and spectrum of tumors that can be successfully removed. Since the introduction of intraoperative monitoring and development of less invasive strategies (e.g., microsurgery, endoscopic surgery, intraoperative navigation, ultrasound, and intraoperative MRI), surgical removal of brain metastases even in deep-seated and elusive areas has become feasible without increased morbidity. To date, the strongest evidence for a survival benefit from surgery is for single CNS metastases.[53] In 1996, Mintz et al.[54] did not confirm a positive impact of surgery on overall survival in these patients. However, only 21.4% of patients in this study had a controlled extracerebral disease, and none of the patients had brain MRI assessment; therefore, comparability with other studies is rather limited. In a retrospective study of treatment modalities in 1,292 patients with CNS metastasis of lung cancer, breast cancer, and melanoma, Lagerwaard et al.[55] demonstrated an increase of median OS of 1.3 months in patients who received best supportive care only, 3.6 months in patients who received RT, and 8.9 months in patients who received a combination of surgery and RT. Similar median OS benefits were also shown in a retrospective study of 1,137 melanoma patients who received best supportive care (2.1 months), RT (3.4 months), surgery (8.7 months), or combined RT and surgical resection.[56]

Benefits of surgery include the ability to establish a tissue diagnosis and an immediate decrease of tumor mass, particularly of masses in the posterior fossa. Nevertheless, patients who might benefit from surgical resection must be carefully selected. Predictors that favor a surgical benefit include: single or few metastases, tumor location, surgical accessibility, KPS > 70, patient age < 65 years, local mass effect, control of extracranial disease, and absence of leptomeningeal involvement.[57] Based on the therapy oncology group database, patients of RPA class I are likely to benefit from surgery, whereas patients of RPA class III are not.[40] The primary goal of surgery is either macroscopic gross total resection or decompression dependent on the aforementioned predictors. Intraoperative neurosurgical techniques to maximize resection (e.g., image-guided surgery,[58] ultrasonography,[59] and introduction of fluorescence-guided surgery[60]) and to minimize neurological deficits by electrophysiological techniques[61] improved the likelihood of complete and safe removal of metastases. A combination of surgery plus radiation in patients with up to three CNS metastases can improve survival and preserve functional independence, as outlined in two prospective studies[62,63] and three retrospective studies.[64-66] Several criteria -- including tumor location, medical comorbidities, extracranial disease, and performance status -- may impact individual consideration and risk assessment for surgical resection. This is particularly relevant because evidence from studies in high-grade glioma surgery indicates that a new
postoperative neurological deficit decreases survival up to 3–4 months, and any substantial postoperative complication negatively affects functional status and the patient’s ability to undergo subsequent radiation treatment, both of which are crucial factors in determining survival. [66]

The main modalities in radiation therapy include stereotactic radiotherapy and whole brain radiation therapy. Stereotactic radiotherapy alone might be considered for patients who have a controlled systemic disease and a limited number of CNS metastases whose size is less than 3 cm. A combination of stereotactic and whole brain radiotherapy has been investigated in large clinical trials. There was no difference in overall survival, but the addition of whole brain radiation therapy significantly improved local and distant control. [9,67] Yet, patients treated with whole brain and stereotactic radiation therapy were at higher risk of a decline in learning and memory. Of note, neurocognitive testing was only performed once at 4 months in this trial. [68]

Novel concepts of whole brain radiation therapy with an avoidance of the hippocampal region might lead to new opportunities in this treatment modality.

Radionecrosis can occur, typically within the first year after stereotactic radiotherapy. The differentiation between tumor progression and radionecrosis might be difficult, as mentioned earlier. Treatment recommendations for radiosurgery radionecrosis include bevacizumab and/or steroids. [69]

Regarding a refinement of treatment planning for radiation therapy, the value of amino acid PET in stereotactic radiotherapy treatment planning for focal recurrence at a previously irradiated site of a brain metastasis was evaluated. In 88 patients, the authors found that the total irradiation volume was significantly smaller in the PET group and that the median survival time was significantly longer in the PET group (18.1 months) than in the MRI planning group (8.6 months). [70]

### CYTOTOXIC CHEMOTHERAPY: NO CONVENTIONAL STANDARD REGIMEN FOR CENTRAL NERVOUS SYSTEM METASTASES

To date, standard cytotoxic chemotherapy regimens have not been defined for the treatment of CNS metastases. Instead, inoperable patients are treated using the same cytotoxic chemotherapy employed for the treatment of extracranial disease. Alternatively, cytotoxic agents with good CNS penetration (such as topotecan, irinotecan, procarbazine, and carboplatin, temozolomide, or fotemustine) are also employed for empirical therapy, even in cases in which these agents are not the standard therapy for the primary tumor site. Pharmacological treatments for intrathecal therapies are ill-defined, too.

### INTRATHECAL TREATMENT THERAPY FOR TARGETING THE CEREBROSPINAL FLUID

Intrathecal administration of drugs aims at targeting tumor cells in the CSF efficiently by circumventing the blood-CSF barrier while omitting systemic toxicity. Treatment can be done by repetitive lumbar punctures or through intraventricular catheter systems (i.e., Rickham or Ommaya reservoir). Among the drugs available for intrathecal treatment, methotrexate (MTX) and cytarabine are most frequently used. Alternatively, thiotriethylenephosphoramide has been approved in some countries. Liposomal cytarabine is a sustained-release form of cytarabine and was compared with MTX in a controlled trial in patients with solid tumors and leptomeningeal carcinomatosis. Patients who were treated with liposomal cytarabine experienced a longer time until neurological progression. However, there was no difference in overall survival. [71] Liposomal cytarabine is associated with an increased risk for radiculitis and arachnoiditis. This might be prevented by prophylactic dexamethasone application.

<table>
<thead>
<tr>
<th>Molecular target</th>
<th>Compound</th>
<th>Compound characteristics</th>
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<tbody>
<tr>
<td>HER2</td>
<td>Trastuzumab</td>
<td>Humanized mAb targeting the extracellular domain of HER2</td>
</tr>
<tr>
<td></td>
<td>Trastuzumab emantitine</td>
<td>Antibody-drug conjugate; the antibody targeting HER2 is conjugated with an antimitotube agent that is only released in HER2 target cells</td>
</tr>
<tr>
<td></td>
<td>Lapatinib</td>
<td>Small molecule tyrosine kinase inhibitor that dually targets HER1 and HER2, binding to the intracellular domain</td>
</tr>
<tr>
<td></td>
<td>Neratinib</td>
<td>Irreversible inhibitor targeting the catalytic domain of EGRF, HER2, and HER4</td>
</tr>
<tr>
<td>EGFR</td>
<td>Gefitinib</td>
<td>Inhibitor of EGFR</td>
</tr>
<tr>
<td>ALK</td>
<td>Erlotinib</td>
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<td>Crizotinib</td>
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<td></td>
<td>Alectinib</td>
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<tr>
<td>BRAF</td>
<td>Vemurafenib</td>
<td>Selective inhibitor of mutated BRAFV600E</td>
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<td></td>
<td>Dabrafenib</td>
<td>Inhibitor of mutated BRAF, wild-type BRAF, and CRAF</td>
</tr>
<tr>
<td>CTLA4</td>
<td>Ipilimumab</td>
<td>Antibody targeting CTLA-4</td>
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<tr>
<td>PD-1</td>
<td>Pembrolizumab</td>
<td>Antibody targeting PD-1 receptor</td>
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<td></td>
<td>Nivolumab</td>
<td>Antibody targeting PD-1 receptor</td>
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Supportive therapy aims at symptom relief. Steroids may help to decrease symptom burden similar to the situation in solid tumor manifestations in the brain.[72]

**TARGETED THERAPIES ARE AVAILABLE FOR A SUBSET OF CENTRAL NERVOUS SYSTEM METASTASES**

With increasing insight into molecular alterations and improved CNS penetration of targeted compounds, some specific molecular-targeted compounds are available that can also be applied in CNS metastases [Table 2]. We focus here on breast cancer, lung cancer, and melanoma.

**Breast cancer**

HER2 is overexpressed in up to 30% of breast cancers.[73] A retrospective analysis of 9,524 women in the pre-trastuzumab era identified HER2 expression as a risk factor for brain metastases[74] with an incidence of CNS metastases in HER2-positive patients twice that of unselected breast cancer patients. Additionally, an increasing percentage of patients develop brain metastases, whereas their systemic disease is controlled using HER2-directed therapies.[75] A retrospective case series reported 23 of 93 (25%) patients developed brain metastases after trastuzumab therapy, and 78% of those patients had stable or better systemic disease. A meta-analysis using data from three large phase III trials indicated the incidence of CNS disease was significantly higher in the trastuzumab-treated patients.[76] A retrospective analysis of 9,524 women in the pre-trastuzumab era identified HER2 expression as a risk factor for CNS recurrence. In a prospective study of 89 patients with NSCLC treated with stereotactic radiation therapy for CNS metastases, the addition of targeted therapies was associated with significantly better outcomes. Patients treated with targeted therapy against EGFR or ALK had a median survival of 21 months compared with 11 months for patients who did not receive targeted therapy.[81] EGFR mutations are present in 10-25% of NSCLC. EGFR mutations in patients with brain metastases may be more common; two reports found EGFR mutations to be present in 63% and 50% of patients, raising the question whether EGFR mutations lead to an increased risk of developing brain metastases similar to HER2 overexpression in breast cancer.[82] Patients with ALK activation, on the other hand, had no increased risk of brain metastases but did show a higher frequency of liver metastases.[83,84]

Neratinib is an orally administered inhibitor of the ErbB receptor tyrosine kinase with antitumor activity in advanced HER2-positive breast cancer.[79] A phase II trial is currently underway for patients with HER2-positive breast cancer and brain metastases (NCT01494662). Further aspects of CNS metastases in the breast are outlined in a recent review.[85]

**Non small-cell lung cancer**

With the discovery of targetable molecular alterations in the treatment of non small-cell lung cancer (NSCLC), patients with newly diagnosed disease are currently stratified based on molecular alterations of several genes in the primary tumor, including the epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene homolog (KRAS), and translocations involving the echinoderm microtubule-associated protein like 4 (EML4) analastic lymphoma kinase (ALK) genes.[86] In a retrospective study of 89 patients with NSCLC treated with stereotactic radiation therapy for CNS metastases, the addition of targeted therapies was associated with significantly better outcomes. Patients treated with targeted therapy against EGFR or ALK had a median survival of 21 months compared with 11 months for patients who did not receive targeted therapy.[81] EGFR mutations are present in 10-25% of NSCLC. EGFR mutations in patients with brain metastases may be more common; two reports found EGFR mutations to be present in 63% and 50% of patients, raising the question whether EGFR mutations lead to an increased risk of developing brain metastases similar to HER2 overexpression in breast cancer.[82] Patients with ALK activation, on the other hand, had no increased risk of brain metastases but did show a higher frequency of liver metastases.[83,84]

Gefitinib and erlotinib are oral compounds and irreversible inhibitors of the intracellular domain of EGFR. Gefitinib is FDA-approved for NSCLC with EGFR mutations. Erlotinib is approved for locally advanced or metastatic NSCLC that has failed at least one prior chemotherapy regimen or for maintenance treatment for locally advanced metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. There is concern about poor BBB penetration of these agents as CNS response rates are disproportional to systemic response rates. Serum to CSF comparisons for gefitinib revealed only about 1% of the serum dose represented in the CSF.[85] Both drugs are near the 400 kDa molecular weight range, with the BBB retaining selectivity for molecules greater than 200-400 kDa. Despite concerns for optimal bioavailability, gefitinib and erlotinib have been investigated in first-line palliative and combination settings. Two phase II trials for tyrosine-kinase inhibitors (TKI) in the first-line setting include data on patients with CNS metastases.[86,87] Both studies do not include sequencing data for EGFR mutations but instead use the clinical indicator of never-smokers. Lee et al.[86] reported 36 never-smoker patients including 10 patients with synchronous brain metastases. Seven of ten patients demonstrated an intracranial objective response to
gefitinib, one patient had stable disease, and two patients had progressive disease after a median of 48-week follow-up period. Kim et al. reported 23 never-smoker patients with synchronous brain metastases with a response rate to either gefitinib or erlotinib of 69% and a disease control rate of 82%. The median overall survival was 18.8 months, and time to salvage WBRT averaged 19.3 months.

Further evidence for first-line TKI comes from a retrospective analysis of 155 patients screened for EGFR mutations. The rate of CNS progression was lower in EGFR-mutant patients with advanced NSCLC treated initially with erlotinib or gefitinib compared with upfront cytotoxic chemotherapy (33% vs. 48%) at a median follow-up of 25 months, supporting a role for these drugs in prevention of CNS metastases. Median overall survival, on the order of 30 months, was not different between the two groups.

Erlotinib in combination with WBRT was evaluated in a prospective phase II trial in 40 patients with brain metastases from NSCLC regardless of EGFR status. The overall response rate was 86% and the median overall survival was 11.8 months. Of these 40 patients EGFR status was known in 17 patients. Interestingly, patients negative for EGFR mutations had a median overall survival of 9.3 months, whereas patients who were positive for EGFR mutations had a median overall survival of 19.1 months. The clinical benefit and feasibility of targeting ALK was demonstrated first with the multitargeted tyrosine kinase inhibitor crizotinib that competitively binds to the ATP-binding pocket of the ALK and MET tyrosine kinases and inhibits phosphorylation of activated ALK. This was subsequently confirmed in phase II and III trials. The ability of ALK-directed therapies to control and prevent the development of CNS metastases remains incompletely studied, with early reports suggesting inefficient CSF penetration of crizotinib.

Ceritinib is a second-generation ALK inhibitor with increased activity against common ALK point mutations. The activity of ceritinib in ALK+ NSCLC has been confirmed in phase I and II studies. Larger head-to-head trials such as the phase III, ALEX “trial comparing alecrtinib to crizotinib will directly investigate PFS in the CNS and may provide further information to inform treatment decisions for ALK+ patients with brain metastases.

**Melanoma**

Activating BRAF mutations affect up to 60% of melanoma patients; more than 95% are the p.V600E mutation, with the remainder largely being p.V600L. Constitutive BRAF signaling activates the mitogen-activated protein kinase (MAPK) pathway. Vemurafenib is an FDA-approved BRAF inhibitor. In a pilot study of 24 patients with melanoma metastatic to the CNS treated with vemurafenib, median PFS was 3.9 months, and median OS was 5.3 months. An overall partial response rate at both intracranial and extracranial sites was achieved in 42%, and stable disease was achieved in 38%. Further data are available from individual cases and population-based studies. New trials with CNS metastases are ongoing. Dabrafenib is an oral ATP-competitive inhibitor of BRAF kinase. A multivariate clinical trial evaluated dabrafenib in 172 patients both with and without prior brain therapy for BRAF-mutated melanoma metastatic to the brain with confirmed p.V600X mutation. The primary outcome measure was overall response rate observed to be 29/74 (39.2%) in patients without prior brain therapy and 20/65 (30.8%) in patients with prior brain therapy. Thus, dabrafenib was helpful in patients with both new and pretreated brain metastases. Duration of response was 20.1 weeks for patients without prior brain treatment and 28.1 weeks for patients with prior brain treatment. Median overall survival was 33 weeks in patients without prior brain therapy and 31 weeks with prior brain therapy.

Resistance to therapy with BRAF kinase inhibitors is associated with a reactivation of the MAPK pathway. Consequently, the combination of BRAF and MEK inhibitor was assessed and showed increased efficacy compared to BRAF monotherapy alone.

Current immunotherapy approaches focus mainly on checkpoint inhibitors Ipilimumab and PD1/PDL1 inhibition. Ipilimumab is a humanized monoclonal antibody against cytotoxic T lymphocyte antigen-4 (CTLA-4); it shows activity in melanoma brain metastasis, particularly if asymptomatic, by improving overall survival, and inhibiting progression-free survival of 4.3 months, with increased incidence in hematological and nonhematological toxicity. Clinical trials for the assessment of immune checkpoint inhibition strategies in CNS metastases are ongoing.

**QUALITY OF LIFE AND NEUROCOGNITION**

The systematic assessment of neurocognitive function is often neglected in clinical routine but is crucial, mainly because neurocognitive function is a key feature of quality of life for patients. It is important to raise awareness and encourage more frequent use of neurocognitive monitoring tools (not only in large centers) as a regular part of the diagnostic workup. Certainly, there are multiple reasons for cognitive decline in patients with CNS metastases, including the neuroanatomical location of the lesions, symptomatic seizures, depression, distress, and potentially also the effects of neurotoxic systemic therapies and whole brain radiation therapy. It is notable that corticosteroids are a very common cause of neurocognitive decline. Steroid-induced changes in mood and sleep certainly affect cognitive function, leading to measurable effects on...
declarative memory and even to decreased hippocampal volumes. The severity of memory impairment is correlated to dose and duration of use.

Primary prevention strategies might include the implementation of hippocampal-sparing whole brain radiation therapy, prophylactic use of the N-methyl-D-aspartate receptor modulator memantine, or blocking the RAAS cascade. Assessment and treatment of depression is an important strategy, including appropriate pharmaceutical or psychological treatments.

**FUTURE PERSPECTIVES**

With increasing incidence of CNS metastases, an improvement of existing treatment strategies is urgently needed. Important steps for meeting this important epidemiological challenge include systematic interdisciplinary multiprofessional treatment teams, thorough biosampling and biobank studies for the establishment of further biomarkers or therapeutic targets, innovative imaging tools, and innovative clinical trial designs with meaningful endpoints including survival, quality of life, and neurocognitive assessments. Any extension of progression-free or overall survival for these patients will only be meaningful if quality of life and neurocognition can be preserved. There is rising need for further definition of reliable molecular/genetic tumor markers to be implemented in routine pathology/neuropathology diagnostics, to catch up to increasing insights into molecular heterogeneity of cancer and its interaction with the local microenvironment.

An important future challenge will be to implement affordable investigations of the molecular and cellular components of the tumor microenvironment. In this regard, it will be increasingly important to visualize and monitor the expression of molecules and cell motion as well as to enhance the technical possibility of calculating cellularity, vessel permeability, vascular perfusion, metabolic and physiological changes, apoptosis, and inflammation prior to and during the course of therapy. A multimodal imaging algorithm is likely to improve sensitivity and specificity to meet these requirements. Certainly, novel multimodal algorithms will have to be prospectively investigated in multicenter trials for validation and standardization.

Since serial tissue biopsies are rarely clinically justified in CNS metastases, and in light of new upcoming targeted treatment options, noninvasive tools to measure drug penetration, pharmacodynamic effects, and efficacy are becoming increasingly important. Examples include PET-based approaches for noninvasive measuring of drug uptake with $^{89}$Zr-trastuzumab and $^{89}$Zr-bevacizumab. Recent studies using magnetic resonance-guided focused ultrasound suggest a role for this noninvasive, radiation-free alternative for treatment of small deep-seated brain metastases. New developments in this field could potentially further expand the treatment spectrum.

For meeting these challenges, interdisciplinary and integrative research strategies must combine clinical investigation, neurological workup, quality of life assessments, neurocognitive testing, imaging, and histological and molecular profiling of tumor tissue to design individualized treatment strategies tailored to patients with CNS metastases. Only then can the full potential of precision therapeutic approaches be exploited for improving outcomes for our patients.

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**Conflicts of interest**

There are no conflicts of interest.

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