Some reports suggest the tide may be turning for this challenging disease.

Experimental Treatments for Leptomeningeal Metastases From Solid Malignancies

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Background: Leptomeningeal metastasis is a consequence of advanced solid malignancies and has limited treatment options. It is possible that it is becoming more common as the leptomeninges act as a sanctuary site for recurrence from systemic cancer.

Methods: Potential targeted and immunotherapy agents for the most common types of solid-tumor leptomeningeal metastasis are reviewed, as are their dosing/delivery strategies and novel, immunological approaches.

Results: Historically, patients with leptomeningeal metastasis have been excluded from clinical trials, and data on the management of leptomeningeal metastasis come from single case reports and retrospective analyses.

Conclusion: For the first time ever, published reports suggest the tide may be turning in this challenging disease.

Introduction

Leptomeningeal metastasis occurs in more than 5% of patients with advanced solid tumors. The most common solid malignancies leading to leptomeningeal metastasis are adenocarcinomas of the breast (12%–35%), adenocarcinomas of the lung (10%–26%), and melanoma (5%–25%). Prognosis is poor for leptomeningeal metastasis: The median overall survival rate after diagnosis is approximately 2 to 3 months.

Improved imaging techniques have resulted in an increased number of diagnosed cases of leptomeningeal metastasis. The advent of targeted drugs and immunotherapies — often with limited penetration into the central nervous system (CNS) — have improved the survival of patients with advanced solid malignancies. However, these advancements have led to an increased prevalence of CNS metastases and leptomeningeal metastases over time. The leptomeningeal compartment has unique features that may allow it to function as a “sanctuary site” for recurrence from systemic cancer. Drugs with poor blood–cerebrospinal fluid (CSF) permeability undertreat the tumoral cells in the subarachnoid space, which can subsequently escape the antitumoral effect and proliferate on the meninges.

Treatment options for patients with leptomeningeal metastasis remain limited: Neither whole-brain radiotherapy nor systemic or intrathecal chemotherapy significantly improves outcomes. In general, patients with leptomeningeal metastasis are excluded from clinical trials because of their poor prognosis and to mini-
mize results that are not reproducible. Thus, treatment data for leptomeningeal metastasis are limited to small case series, thereby limiting our ability to draw conclusions that will apply to patients with leptomeningeal metastasis.

Investigational treatment options (targeted and immunotherapies) that may be beneficial in patients with the most common types of leptomeningeal metastasis are discussed below and also appear in the Table.3-18

**Targeted Therapies**

**Melanoma**

**BRAF Inhibitors:** Several case series and retrospective reviews have shown an intracranial benefit for patients with active brain metastases harboring **BRAF** V600 mutations treated with vemurafenib.4,5,19 An intracranial response rate of 48.1% was reported by Gibney et al.19 However, the activity of vemurafenib in patients with leptomeningeal metastasis is less clear. In 2 patients with tumors harboring **BRAF** V600 mutations, treatment with either vemurafenib alone or in sequence with whole-brain radiotherapy resulted in marked responses and the long-term stabilization of leptomeningeal disease.4,5 Schäfer et al1 studied the drug in a person with leptomeningeal metastasis whose disease was unresponsive to whole-brain radiotherapy. Dosing of vemurafenib was given at 960 mg twice per day. Twelve weeks after the initiation of vemurafenib, the patient had a complete resolution of clinical symptoms, achieved a cytological response in CSF, and had marked radiographic regression of the meningeal lesions on magnetic resonance imaging.4 However, analyses of the CSF concentration of vemurafenib in patients with brain metastases have revealed very low ratios of CSF:plasma concentration (0.98% ± 0.84%) and large rates of interindividual variability.20

Dabrafenib has demonstrated intracranial antitumor activity in patients with **BRAF** V600E or V600K–mutant melanoma brain metastases.21 In a phase 2 trial evaluating dabrafenib in patients with active brain metastases from **BRAF** V600E or V600K–mutant melanoma, the overall intracranial response rates (complete response + partial response) of 39.2% and 6.7% were observed in those with no previous local treatment and **BRAF** V600E or V600K–mutant tumors, respectively.21 These results suggest that dabrafenib can functionally penetrate the disrupted blood–brain barrier within melanoma brain metastases.

Wilgenhof and Neyns3 reported a patient with leptomeningeal metastasis from **BRAF** V600E–mutant melanoma treated with dabrafenib 150 mg twice a day. Complete imaging and cytological response were observed after 4 weeks of dabrafenib and continued at the time of report (15 weeks after the initiation of dabrafenib), suggesting that dabrafenib may have potential benefit in patients with leptomeningeal metastasis from **BRAF** V600E or V600K–mutant melanoma.5

### Table. — Targeted Therapies for Select Patients With Leptomeningeal Metastasis From Melanoma, NSCLC, or Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Tumor Type</th>
<th>Targeted Therapy</th>
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<tbody>
<tr>
<td>Breast Cancer</td>
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<tr>
<td>Ferrario16</td>
<td>ERBB2 positive</td>
<td>Intrathecal trastuzumab</td>
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<td>Platini10</td>
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<td>Stemmler15</td>
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<td>Zagouri18</td>
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<td>Melanoma</td>
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<td>Vemurafenib</td>
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<td>Schäfer4</td>
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<tr>
<td>Wilgenhof3</td>
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<td>Dabrafenib</td>
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<td>NSCLC</td>
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<tr>
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<td>EGFR mutant</td>
<td>High-dose daily gefitinib</td>
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<td>Gainor9</td>
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NSCLC = non–small-cell lung cancer.

**Non–Small-Cell Lung Cancer**

**Epidermal Growth Factor Receptor–Tyrosine Kinase Inhibitors:** High-dose epidermal growth factor receptor–tyrosine kinase inhibitors. High-dose tyrosine kinase inhibitors (TKIs) have been used to treat leptomeningeal metastasis from **EGFR**-mutant non–small-cell lung cancer (NSCLC) based on the hypothesis that higher concentrations in the CSF can be reached by using higher, systemic concentrations of TKI.6,22 Using standard doses of epidermal growth factor receptor (EGFR)–TKIs, CSF concentrations of the drug can be as low as 1% plasma levels below half maximal inhibitory concentration.9,22 Therefore, the CSF concentration of EGFR-TKIs achieved by standard daily dosing may be insufficient for a therapeutic effect.

By contrast, the intermittent “pulsatile” administration of high-dose erlotinib (1500 mg once weekly) has been shown to be well tolerated and does achieve therapeutic drug levels in the CSF.22 With this regimen, concentrations of the drug in the CSF exceeded the half maximal inhibitory concentration for **EGFR**-mutant lung cancer cells in a patient with leptomeningeal metastasis.22

Grommes et al11 reported on a series of 9 patients with **EGFR**-mutant NSCLC who had developed CNS metastases despite conventional daily erlotinib therapy or other EGFR-TKIs. Eight patients had leptomeninge-
al metastasis. Pulsatile erlotinib was administered as monotherapy to all patients at a median weekly dose of 1500 mg (range, 900–1500 mg). Median time to CNS progression was 2.7 months (range, 0.8–14.5 months), and the median overall survival rate was 12 months.

Several reports of patients with leptomeningeal metastasis from *EGFR*-mutant NSCLC have described similar responses with pulsatile high-dose erlotinib or daily high-dose gefitinib. These data suggest that high-dose *EGFR*-TKI therapy can be effective in achieving higher CSF concentrations of the drug and, therefore, may control leptomeningeal metastasis in a subset of patients with *EGFR*-mutant NSCLC.

**Dual-targeting of epidermal growth factor receptor.** Dual targeting of *EGFR* has been reported as a potential therapy for patients with leptomeningeal metastasis from *EGFR*-mutant NSCLC. A phase 1b trial combining afatinib, a second-generation *EGFR*-TKI, and cetuximab observed an objective response rate of 29% in individuals with advanced *EGFR*-mutant NSCLC with systemic disease progression after receiving gefitinib or erlotinib. This result has raised the question as to whether this strategy might be effective in controlling leptomeningeal metastasis in patients with *EGFR*-positive NSCLC.

Lin et al. reported on 1 patient with exon 19 deleted NSCLC who developed leptomeningeal metastasis after 4 years of multiple treatments, including gefitinib and erlotinib. Treatment with 1 month of pulsatile erlotinib, at a dose of 1050 mg weekly, did not control leptomeningeal metastasis, but subsequent treatment with afatinib 40 mg daily and cetuximab 250 mg/m² biweekly resulted in clinical improvement as well as improvement seen on imaging. The improvement in leptomeningeal metastasis remained stable until the patient died from systemic disease progression 4 months later. The authors suggest that dual-targeted therapy may still benefit patients with leptomeningeal metastasis from *EGFR*-positive NSCLC whose disease has progressed on a high-dose TKI.

**Tyrosine Kinase Inhibitors of Anaplastic Lymphoma Kinase in Lung Cancer:** The CNS is a frequent site of relapse among patients with *ALK*-rearranged NSCLC who have been treated with crizotinib. The poor penetration of crizotinib to the brain (“pharmacokinetic relapse”), rather than cellular resistance, has been suspected as the mechanism of treatment failure.

Ceritinib is a potent inhibitor of anaplastic lymphoma kinase (ALK) that has shown significant benefit in *ALK*-rearranged NSCLC refractory to crizotinib therapy. It also has activity in the CNS: Partial responses have been seen in brain metastases among crizotinib-naive and crizotinib-refractory tumors, suggesting possible activity in patients with leptomeningeal metastasis. Arrondeau et al. reported on 1 patient with crizotinib-refractory leptomeningeal metastasis who was treated with daily ceritinib (initially 750 mg and then 600 mg). The patient achieved stable disease seen on imaging and durable clinical improvements that lasted for more than 6 months. However, ceritinib has been shown to cross the blood–brain barrier in rat models at a brain-to-blood exposure ratio (AUC <sub>brain</sub>/AUC <sub>plasma</sub>) of 15%. Although its penetration into the CSF in patients with leptomeningeal metastasis is unknown, CSF concentration is likely higher due to a disrupted blood–CSF barrier in the setting of leptomeningeal metastasis.

Alectinib is a second-generation TKI of ALK that has shown promising CNS activity in study patients with *ALK*-rearranged NSCLC. It is approximately 5 times more potent than crizotinib against ALK, and it inhibits RET with similar potency to ALK. Preclinical studies have suggested that alectinib is not a substrate of P-glycoprotein, a key factor in the blood–brain barrier, and that it achieves high brain-to-plasma ratios (range, 0.63–0.94) in intracranial tumor implantation murine models of *EML4-ALK*-positive NSCLC.

In a phase 2 study of alectinib in crizotinib-refractory ALK-rearranged NSCLC, a complete CNS response rate of 27% was observed. Alectinib also resulted in an overall CNS response rate of 57% in study patients with measurable CNS metastases. Alectinib has shown efficacy in symptomatic individuals who have crizotinib- or ceritinib-refractory leptomeningeal metastasis. In a case series by Gainor et al., alectinib 600 mg twice daily resulted in significant clinical and radiographic improvements in 3 out of 4 of patients with crizotinib- or ceritinib-refractory leptomeningeal metastasis from ALK-rearranged NSCLCs. The fourth patient achieved stable disease for approximately 4 months.

PF-06463922 is an investigational agent with superior potency against all known clinically acquired *ALK* mutations, including the highly resistant G1202R mutant, and is designed to minimize P-glycoprotein–mediated drug efflux and optimize penetration of the CNS. It has shown significant regression of *EML4-ALK*-driven brain metastases in murine models, which led to prolonged rates of survival.

**Breast Cancer**

**Intrathecal Trastuzumab:** *ERBB2* (formerly known as *HER2/neu*)-positive breast cancers have a high affinity for CNS involvement. Better control of systemic *ERBB2*-positive breast cancer with agents such as trastuzumab has led to a higher prevalence of CNS and leptomeningeal metastases. Trastuzumab can be intrathecally administered, either alone or in combination with different chemotherapy agents (eg, methotrexate) and has shown promising results in participants with leptomeningeal metastasis from *ERBB2*-positive breast cancers.
were observed; the patient survived for more than 3 weeks. Complete clinical and radiological responses followed by 4 courses of ipilimumab 3 mg/kg every 3 months. Whole-brain radiotherapy (5 times 4 Gy) was administered. The continued administration of intrathecal trastuzumab beyond disease progression and switching intrathecal chemotherapy agents appeared to be safe and resulted in significant clinical benefit (median CNS progression-free survival of 9.4 months beyond progression). The recommended dosing schedule of intrathecal trastuzumab administration is unknown, and different dosing ranges (e.g., 20–100 mg weekly, 100–150 mg biweekly) have been used with no safety issues. In our experience, intrathecal trastuzumab is a safe and effective therapy for patients with ERBB2-positive breast cancer leptomeningeal metastasis, which can delay the need for whole-brain radiotherapy and provide clinical and cytological improvements as well as improvements seen on imaging.

Immunotherapies

**Checkpoint Inhibitors**

Antibodies against cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death 1 (PD1) have significant activity in extracranial metastatic melanoma. Anti-PD1 and anti–programmed death ligand 1 (PD-L1) antibodies have been approved for the treatment of metastatic melanoma, NSCLC, and renal cell carcinoma and are showing promising results in several other tumor types. Two prospective, phase 2 trials have shown the efficacy of ipilimumab, an anti-CTLA-4 antibody, among patients with melanoma-associated brain metastasis. In a phase 2 study by Margolin et al, ipilimumab monotherapy resulted in a CNS response rate of 16%; a median overall survival of 7 months was observed in those with symptomatic brain metastases. At present, multiple studies are investigating the efficacy of anti-PD-1/PD-L1 antibodies in patients with brain metastases.

Intrathecal Tumor-Infiltrating Lymphocyte Therapy

Adoptive T-cell therapy using autologous tumor-infiltrating lymphocytes (TILs) has emerged as a promising therapy for advanced solid tumors. TIL therapy has resulted in response rates of approximately 50% in patients with refractory melanoma. However, few data are available on the intrathecal administration of TILs in patients with leptomeningeal metastasis. Glitza et al have reported that intrathecal autologous TILs in combination with intrathecal IL-2 were safe and feasible in an individual with refractory leptomeningeal metastasis from melanoma whose disease had progressed after monotherapy with intrathecal IL-2. This patient received 3 doses of intrathecal TILs (0.3 × 10⁶ cells, 1.0 × 10⁶ cells, and 3.0 × 10⁹ cells) 1 week apart; the TILs consisted of 96% CD8+ T cells. Injections of TILs were well tolerated. On days 1 and 4 after intrathecal TILs, intrathecal IL-2 (1.2 million U) was administered. Intrathecal IL-2 was associated with nausea, vomiting, headache, chills, and transient changes in mentation requiring the serial removal of CSF due to elevated intracranial pressure. The radiographic stabilization of leptomeningeal metastasis was observed after intrathecal TIL therapy; however, the therapy did not control the parenchymal brain metastases, which progressed approximately 3 months following therapy.

**Conclusions**

Leptomeningeal metastasis is a major medical complication of systemic cancer that has become more com-
mon as major advances are made in cancer treatments. Paradoxically, our understanding of the mechanisms of the development and biology of leptomeningeal metastasis is poor. The incidence of leptomeningeal metastasis is likely to continue to increase due to improved overall survival of patients with cancer and because of more effective systemic treatments with limited penetrance into the central nervous system. As such, effort should be made to develop novel molecules to improve central nervous system penetration and to optimize drug-delivery methods. Patients with leptomeningeal metastasis are generally excluded from clinical trials, thereby limiting the systematic assessment of novel therapies in this subgroup of patients with poor prognoses. Retrospective analyses involving a heterogeneous group of patients can provide information on possible treatment options that may be used for the treatment of patients with leptomeningeal metastasis; however, no significant conclusions about safety and predicted responses can be drawn with the data currently available. Moving forward, every effort should be made to enroll patients with leptomeningeal metastasis into trials investigating novel agents with the potential to penetrate the blood–brain barrier. The issues of the relatively poor prognosis and the complexity of assessing responses in this patient population may be further addressed by designating specific cohorts for patients with leptomeningeal metastasis from tumor types of interest.

References