Review Article

Targeted therapy for leptomeningeal metastases in non-small cell lung cancer – Changing treatment paradigms

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Abstract

Leptomeningeal metastasis is an uncommon but serious complication in patients with advanced cancers. Leptomeningeal metastasis is diagnosed in approximately 5% of the patients, most commonly among patients with cancers of breast and lung, melanoma, and gastrointestinal malignancies. Treatment goal is to improve survival and quality of the patients. Use of targeted therapies and immunotherapy has led to improved survival of patients with non-small cell lung cancer (NSCLC). In this article, we review emerging data on use of mutation-specific agents and immunotherapy in the treatment of leptomeningeal metastasis among patients with NSCLC.

Keywords: Non-small cell lung cancer; leptomeningeal metastases; immunotherapy

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Introduction

Leptomeningeal metastasis, or leptomeningeal carcinomatosis, is a rare, but often devastating complication arising from the seeding of malignant cells from advanced stage cancers to the leptomeninges. While autopsy studies have confirmed the presence of these metastases in approximately 20% of patients with metastatic cancer, leptomeningeal metastases are currently only diagnosed in about 5% of living patients with existing metastatic disease, most notably cancers of the breast and lung, melanoma, and gastrointestinal malignancies (1). This suggests that patients may have non-specific symptoms until the disease has progressed to a late stage, making a high index of clinical suspicion crucial in early diagnosis and successful treatment. This is especially pertinent due to the rising incidence of this complication, most likely associated with increased survival time with improved treatment protocols (1).

Leptomeningeal metastases involve tumors of the inner layers of the meninges and the subarachnoid space, in which the cerebrospinal fluid (CSF) circulates. They can be categorized into two types: diffuse type, which involves non-adherent cells without contrast-enhancing nodular lesions in subarachnoid space; or nodular type, characterized by contrast-enhancing leptomeningeal tumor nodules (2). Identifying the differences between these types may help guide treatment methods.

Treatment goals are also specific to the location and severity of metastasis. Primary treatment goals include both prolonged survival and symptomatic relief from neurological involvement, as well as restoration of satisfactory quality of life. Stratifying patients into risk categories based on parameters such as Karnofsky performance status, neurological deficits, and extent of systemic disease can be helpful in driving treatment course. In severe cases, palliative care is favored over aggressive treatment. There is currently no standard of treatment due to the limited data in the literature secondary to rapid progression and relative rarity of the disease.

In patients with non-small cell lung cancer (NSCLC), the incidence of leptomeningeal metastasis is approximately 3.8%, with about a third of these patients having concomitant brain metastases (3). The median overall survival for these patients is between 3.6 to 11.0 months, using modern treatment modalities (3). One of the challenges of chemotherapy is adequate penetration of the blood-brain barrier into the central nervous system (CNS). This may explain why traditional chemotherapy is often ineffective in patients with CNS metastases. Identifying NSCLC patients with specific driver mutations, which are currently found in about 20%–25% of these patients, allows for treatment with targeted therapies tailored toward their mutation, which could increase efficacy. These therapies may also be used in patients where traditional chemotherapy is not an option. The most common mutations seen are *KRAS* mutation (29%), epidermal growth factor receptor (*EGFR*) mutation (11%), anaplastic lymphoma kinase (*ALK*) rearrangement (5%), and *MET* mutation (4%) (4). We will discuss some of these mutations in NSCLC patients with leptomeningeal metastases and provide an overview of emerging advancements in mutation-specific therapies.

EGFR mutations

EGFR mutations are a dominant subtype of NSCLC and account for about 10% of lung cancers in the Caucasian population and up to 50% in the Asian population, with an average survival of 3.1 months (5). The incidence of leptomeningeal metastases in *EGFR*-mutant NSCLC is significantly higher than *EGFR*-wild-type NSCLC (9.4% *vs*. 1.7%, P<0.001) (5). EGFR tyrosine kinase inhibitors (TKIs) are the standard of care in this population as they have improved response rates and superior progression-free survival (PFS) and quality of life to traditional chemotherapy (6). One of the advantages of EGFR-TKIs is their superior CSF penetration compared to traditional systemic chemotherapeutic agents. Their efficacy is proven by retrospective studies which show an average improvement in overall survival of 19 months (5).

First-generation EGFR-TKIs, erlotinib and gefitinib, are currently used as first-line treatments. Both drugs have similar toxicity profiles, but there may be some differences in terms of efficacy (7). Several studies have disease control with erlotinib following progression of disease on gefitinib (8-10). Erlotinib has also been shown to have better CSF penetration and higher concentrations in the CSF (11). Togashi *et al*. examined 15 patients and found that CSF concentration and penetration ($\bar{x} \pm s$) of erlotinib were 28.7±16.8 ng/mL and 2.77%±0.45%, compared to gefitinib, which had a CSF concentration and penetration of only 3.7±1.9 ng/mL and 1.13%±0.36% (12). A retrospective review of 25 patients with leptomeningeal metastases and EGFR-positive NSCLC also found that erlotinib was more effective in clearing malignant cells from the CSF than gefitinib (13). These data suggest that erlotinib may have better control of leptomeningeal metastases in EGFR-positive NSCLC than gefitinib.

There are several mechanisms that lead to acquired resistance to EGFR-TKIs, including T790M mutation and c-Met amplification (5). These changes are seen in over 50% of patients after first-generation TKI failure (5). Newer generations of EGFR-TKIs have been devised that are effective in NSCLC patients who have developed resistance to first-generation EGFR-TKIs. Afatinib is a second-generation EGFR-TKI that has shown superior CNS response and has been shown to be effective even after TKI failure (14).

This was shown by Hoffknecht *et al*., who examined 541 patients in the afatinib compassionate use program. There are scant data in the established literature about the penetration rates of afatinib, but Hoffknecht *et al*. reported that the CSF-to-plasma ratio was 0.69% in one patient (14). The data, however, indicate that despite the lower ratio, afatinib achieves concentrations high enough to have a clinical effect.

Osimertinib is a third-generation EGFR-TKI that has been approved by the Food and Drug Administration (FDA) for use in patients with *EGFR* T790M mutation (15). The collective evidence suggests that osimertinib has higher efficacy and penetration than first-generation EGFR-TKIs. For example, in preclinical trials, Ballard *et al*. demonstrated that the distribution of osimertinib was approximately 10-fold higher than gefitinib (16) and Nanjo *et al*. demonstrated five times higher CSF efficacy than erlotinib (17). Phase I and II BLOOM trials have also shown its efficacy, measured by radiological improvement and control of leptomeningeal metastases (18). Phase III (AURA3) studied 419 patients with *EGFR*-mutant NSCLC who had progression of disease with first-line therapy. In these patients, treatment with osimertinib had significantly greater efficacy than traditional chemotherapy, including longer median PFS (10.1 months *vs*. 4.4 months, P<0.001), and higher objective response rates, 71% in osimertinib group [95% confidence interval (95% CI), 65%–76%] and

31% in the platinum-pemetrexed group (95% CI, 24%–40%), with lower incidence of adverse effects leading to permanent discontinuation (19). Furthermore, this study also examined CNS metastases and demonstrated that osimertinib had better results than platinum-pemetrexed. The hazard ratio for PFS also favored osimertinib specifically in patients with CNS metastases (median PFS: 8.5 months *vs*. 4.2 months, with a hazard ratio of 0.32; 95% CI, 0.21–0.49) (19). These results are particularly encouraging in NSCLC patients with suspected or diagnosed leptomeningeal metastases.

Combination therapy with EGFR-TKIs and bevacizumab, which is directed at vascular endothelial growth factor A (VEGF-A) also used in NSCLC, has also been shown to be effective in patients who have failed monotherapy with erlotinib alone. Ariyasu *et al*. found that the combination of erlotinib and bevacizumab showed improved efficacy in two case studies, including decreased radiographic activity and improved symptom control (20). Sakata *et al*. found similar improved performance status and CSF penetration in one patient treated with this same combination. In this patient, CSF penetration of erlotinib was found to be 5.4%, much higher than the reported average CSF penetration of 1.13%±0.36% with erlotinib alone (12,21). Furugaki *et al*. also found improvement in anti-tumor activity with the combination of bevacizumab to erlotinib, but only in the subset of patients with c-Met amplification and only in those who were already sensitive to erlotinib alone (22). Combinations with gefitinib and bevacizumab have also been shown to be well-tolerated and effective. In a single-arm phase II trial in treatment-naïve patients, Ichihara *et al*. showed that this combination therapy had improved PFS and tolerable toxicity (23). Yet another trial is currently ongoing, examining osimertinib and bevacizumab for EGFR-mutant NSCLC (NCT02803203). These preliminary data show that combination therapies with bevacizumab and EGFR-TKIs are a promising strategy to penetrate the blood-brain barrier. Larger trials and prospective studies are warranted.

Research is also being done on the efficacy and tolerability of pulsatile and high-dose EGFR-TKI treatments. A study conducted by Kawamura *et al*. showed that NSCLC patients with refractory CNS metastases responded to high-dose erlotinib (300 mg/d *vs*. standard dose 150 mg/d) (24). Out of 10 evaluable patients with leptomeningeal metastases, 3 showed MRI response, 4 showed improvement in performance status, and 6 showed an improvement in neurological symptoms (24). Furthermore, median survival was improved from 5.8 to 6.2 months (24). Jackman *et al*. demonstrated that patients receiving high-dose gefitinib had improvement in neurological symptoms and achieved higher CSF concentrations than with standard dose gefitinib (250 mg/d) (25). They recommended, in areas where clinically available, 750 mg daily for 14 days followed by 500 mg for 15 days in *EGFR*-mutant positive NSCLC patients with leptomeningeal metastases. Data on high-dose, pulsatile therapy are also promising. A recent case study by Kanemaru *et al*. examined a 64-year-old woman with *EGFR*-mutant leptomeningeal metastases who had progression of disease on several regimens, including erlotinib and rechallenge with gefitinib. High-dose, pulsatile erlotinib therapy (1,050 mg weekly) was well-tolerated and the patient had improvement in neurological symptoms (26). These data suggest that further research and prospective trials regarding tolerability and efficacy of pulsatile and high-dose EGFR-TKIs may be beneficial in establishing additional treatment regimens for treating *EGFR*-mutant patients with leptomeningeal metastases.

New EGFR-TKIs that effectively penetrate the blood-brain barrier are also being developed. AZD3759 is a novel EGFR-TKI that has been shown to have 100% CSF penetration. In 29 patients, it was shown to have equal plasma and CSF concentration with no adverse drug-related CNS effects (27). In another study, among five patients with leptomeningeal metastases, four had >50% tumor cell decrease in the CSF and one had complete CSF clearance of tumor cells as well as improvement on brain magnetic resonance imaging (MRI) and CNS symptoms (28). Other adverse effects were similar to that of the existing EGFR-TKIs. These results are reassuring and further clinical study regarding tolerability, dose escalation, comparisons between these novel agents and older EGFR-TKIs is ongoing.

ALK rearrangement

The *ALK* gene encodes the ALK tyrosine kinase receptor. Some of these mutations involve translocation and fusion with the echinoderm microtubule associated protein like 4 (*EML4*) gene and have been identified in patients with NSCLC (29). Leptomeningeal metastases are seen in about 5% of *ALK*-mutant NSCLC patients and take, on average, 9 months to develop (6).

Crizotinib, a first-generation ALK inhibitor, is currently being used as the standard first-line treatment for *ALK*-

rearranged NSCLC. The PROFILE 1007 and 1014 trials found that crizotinib had better outcomes than standard chemotherapy (30,31). Resistance was commonly seen within one to two years of treatment initiation (29). Furthermore, crizotinib showed poor activity against CNS metastases. This may be due to the low blood-brain penetration of most ALK-TKIs, including crizotinib, which has a CSF penetration rate of 0.26% (32). Despite these difficulties, a 2016 study by Johung *et al*. showed that combination therapy with ALK-targeted TKIs and whole-brain radiotherapy had increased survival and PFS (33).

Second-generation ALK inhibitors have been developed in response to the development of resistance to crizotinib. Ceritinib is a second-generation ALK inhibitor that is 20 times more potent than crizotinib and has been studied in patients who have failed crizotinib therapy. Phase I of the ASCEND trial found ceritinib to be highly active and have improved treatment measures in *ALK*-mutated patients who had failed crizotinib therapy (34). These results have been confirmed in the single-arm, open-label, multicenter trials of phase II ASCEND-2 (NCT01685060) and ASCEND-3 (NCT01685138). While the CNS penetration rate of ceritinib and CSF concentrations of ceritinib have not been fully investigated, these trials have had similar CNS and systemic response rates, as well as promising increases in PFS. The currently ongoing ASCEND-7 trial, an open-label, five-arm study, will further determine the efficacy and safety of oral ceritinib in *ALK*-mutant NSCLC patients, including those with leptomeningeal metastases.

Alectinib is another highly-selective ALK inhibitor that has been found to be more potent and effective than crizotinib, and has had a higher CNS response rate than crizotinib (35). Again, CNS penetration rates and CSF concentrations have not been fully studied. However, a multicenter, single-arm, open-label phase I-II study found alectinib to be highly active and well tolerated in patients with advanced, *ALK*-mutant NSCLC (36). Nokihara *et al*. also compared alectinib to both critozinib and ceritinib and found superior results with alectinib in terms of efficacy and safety in the open-label phase III J-ALEX study (37). Another study examined four *ALK*-rearranged NSCLC patients with leptomeningeal metastases who had failed either crizotinib or ceritinib and found that three had significant clinical and radiological improvements with alectinib and one had stable CNS disease for four months before systemic disease progression (38). Dose escalation after progression of leptomeningeal metastases on standard dosing has also been studied. Gainor *et al*. found that increasing the dose of alectinib from 600 mg twice a day to 900 mg twice a day resulted in improved clinical and radiological responses (39). This suggests that further study of the dosing of alectinib may be required, specifically to evaluate CNS inhibition and to investigate maintenance of control of disease progression.

Another potent second-generation ALK inhibitor that has been developed is brigatinib. In an ongoing, single-arm, open-label phase I/II study, 137 *ALK*-mutant NSCLC patients who had failed all currently available therapies were evaluated for the efficacy and safety of brigatinib (40). So far, improvement in clinical activity has been encouraging and the safety profile has been within acceptable limits (40). The antitumor activity of this second-generation ALK inhibitor is seen both systemically as well as with brain metastases. More trials are underway, comparing brigatinib to other therapies. For example, the ALTA-1L phase III study is currently recruiting participants to compare the efficacy of brigatinib *vs*. crizotinib (NCT02737501).

Third-generation ALK inhibitors are currently being developed specifically to optimize CSF penetration. Lorlatinib (PF-06463922) is novel, small molecule ALK and ROS1 inhibitor that has demonstrated effectiveness even in resistant *ALK*-mutant NSCLC. In a phase I/II clinical trials, it has demonstrated a decrease in intracranial symptoms and has even resensitized one patient to crizotinib after failing lorlatinib treatment, indicating that retreatment may be an option (29). Further progressive trials are necessary to evaluate this clinically. Additionally, a phase II trial, currently recruiting patients, is evaluating the safety and efficacy of lorlatinib in ALK-positive, advanced NSCLC patients, including those with intracranial disease progression (NCT01970865). Data from these trials will help evaluate whether these novel agents have the potential for treating leptomeningeal metastases that is refractory to currently available therapies.

BRAF and *HER2* mutations

BRAF is a proto-oncogene that encodes a component of the mitogen-activated protein kinase (MAPK) pathway. Mutations lead to constitutive kinase activation and ultimately, unregulated cellular growth. These mutations represent approximately 2%–4% of lung cancers (41). The most common *BRAF* mutation in lung cancer is the V600E subtype, which represents about 50% of this population and is the aim of many targeted therapies (41).

A retrospective study of 27 patients showed that vemurafenib, a B-Raf inhibitor, had a 50% intracranial response rate and a 71% extracranial response rate, with one-year overall survival of 30.4% (42). A case study of one patient with metastatic NSCLC also showed improvement in visceral disease and regression of intracranial disease in response to vermurafenib treatment (43). These studies suggest that vemurafenib has sufficient penetration of the blood-brain barrier and may be effective against CNS disease, including leptomeningeal metastases, in those with *BRAF* mutations. Further study is warranted.

The FDA recently granted approval to the combination trametinib and dabrafenib, another B-Raf inhibitor, for treatment in patients with V600E-mutated metastatic melanoma. In a double-blind, placebo-controlled phase 3 trial with 870 patients with resected stage III melanoma, 3-year relapse-free survival was 58% in the combination-therapy group and 39% in the placebo group (95% CI, 0.39–0.58; P<0.001) (44). Additionally, the 3-year overall survival rate and rates of metastasis-free survival were higher in the combination-therapy group (44). Retrospective studies have also shown that in conjunction with radiation therapy, B-Raf inhibitors may improve outcomes (45,46). Further research is needed on the effect of these therapies specifically concerning leptomeningeal metastases. The current research on vemurafenib and recent approval of this combination therapy by the FDA seem to be emerging as promising targeted treatment options for advanced *BRAF*-mutated NSCLC with CNS metastases.

Human epidermal growth factor 2 (*HER2*) mutations, usually associated with breast cancer, are only associated with 2%–5% of lung cancers (47). However, this mutation is associated with an increased incidence of CNS metastases in both breast and lung cancers (48). Trastuzumab is used in HER2-positive cancers, but like other monoclonal antibodies they have limited penetration of the blood-brain barrier and are therefore primarily used for control of systemic disease (49). It has been evaluated as an antibody-drug conjugate with the cytotoxic compound, emtasine, in order to increase CNS penetration. In 2015, a retrospective trial showed that trastuzumab-emtasine, also known as T-DM1, was associated with increased overall survival (26.8 months) in those with CNS progression in advanced HER2-positive breast cancer compared to capecitabine-lapatinib (50). Additional studies including NSCLC patients with leptomeningeal metastases are necessary to make conclusions about the role of trastuzumab antibody-drug conjugates such as T-DM1 in this population.

Targeted Immunotherapy

Recent advances have been made in the development of therapies utilizing immunomodulating antibodies against malignant tumors. Programmed cell death protein-1 (PD1) is a cell surface receptor that promotes self-tolerance and have been a target of antibodies in immunotherapy treatment.

A randomized phase III study compared the efficacy of pembrolizumab, an anti-PD1 antibody, against platinum-based chemotherapy in patients with advanced NSCLC. It was shown to be more effective in both overall survival and PFS than platinum-based chemotherapy (51). Additionally, Goldberg *et al*. describes a non-randomized, open-label, ongoing phase II trial that examined pembrolizumab in 18 patients with CNS metastases from NSCLC and found that all but one patent showed ongoing response over the course of one year of treatment (52). While many studies have looked at immunotherapy in systemic treatment, additional studies examining intracranial activity of targeted immunotherapy and studies involving NSCLC patients with advanced leptomeningeal metastases are necessary. More prospective trials will help in determining treatment protocols and safety of immunotherapy in CNS metastases.

Conclusions

Leptomeningeal metastases are a devastating complication, represented in patients with many types of primary cancer including NSCLC, with incidences that may reach up to 20%. Although systemic and targeted therapies are being studied in detail, prognosis remains poor. One of the main obstacles thus far has been the ability for systemic therapy to penetrate the blood-brain barrier to physically reach these metastases. This has become the growing focus of current research in the development of therapies for leptomeningeal and other CNS metastases. Personalized therapies that are precisely designed to penetrate the CSF and target these specific mutations, including *EGFR* and *ALK* variants, have shown increased survival and better safety profiles over non-selective treatment. At this point, further research is warranted to define precise dosages and standard protocols in the treatment for patients with leptomeningeal metastases. With the recent advances in treatment methods, the prognostic outlook of these

metastases is looking more promising.

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Footnote

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