REVIEWS

Central nervous system penetration and efficacy of targeted therapies used in non-small cell lung cancer and melanoma with brain metastases

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ABSTRACT

Recently, many targeted therapies have been approved for treating brain metastases in non-small cell lung cancer and melanoma patients. In this article, the targeted therapies and their mechanism of action will be reviewed. It will highlight the central nervous system penetration of the targeted therapies. The article will also relate the efficacy of these drugs as seen in clinical trials, which would help guide clinicians when managing these patients.

Key Words: Non-small cell lung cancer, Melanoma, EGFR inhibitor, ALK inhibitor, BRAF inhibitor, MEK inhibitor, VEGF inhibitor, Immunotherapy

1. INTRODUCTION

Currently, the FDA has approved many targeted therapies for non-small cell lung cancer and melanoma associated with brain metastases. These targeted therapies inhibit specific molecules such as EGFR, ALK, VEGF, BRAF, and MEK. Additionally, immunotherapy is also being utilized for treating brain metastases. These drugs provide a novel way to treat brain metastases, which has historically been treated with local surgery, stereotactic radiosurgery, or whole brain radiation therapy.[1] Since these treatments have side effects and delay systemic therapy, the treatment with the newer targeted therapies is ideal. This article will focus on the targeted therapies, their mechanism of action, central nervous system (CNS) penetration and efficacy.

2. NON-SMALL CELL LUNG CANCER (NSCLC)

The targeted therapies which are used for advanced NSCLC act on the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) receptors and vascular endothelial growth factor (VEGF).

2.1 EGRF inhibitors

2.1.1 *Erlotinib*

Erlotinib is an EGFR inhibitor and is used as a first line treatment for NSCLC. It competes against ATP to reversibly bind to the catalytic domain of the EGFR. This blocks signal transduction events and potential tumorigenic effects.[2] Erlotinib and its active metabolite OSI-420's CNS penetration was assessed in four patients with NSCLC. They were

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given 150 mg of erlotinib. The results showed that erlotinib CSF concentration was 5.1% and OSI-420 CSF concentration was 5.8%. Therefore, erlotinib maybe a good treatment option for NSCLC with brain metastases.[3] Additionally, Togashi et al. stated that erlotinib's CSF concentration increased with its plasma concentration, which could be useful in cases of refractory CNS metastases in NSCLC patients. This suggests that erlotinib administered at a higher dose than 150 mg, could be beneficial.[4] In a retrospective study by Bai et al., 40 patients with advanced NSCLC were given erlotinib. In the patients with intracranial disease, 4 (10%) had partial response, 21 (52.5%) had stable disease, and 15 (37.5%) had progressive disease. The patients with EGFR mutations had a disease control rate of 80%. The study showed that erlotinib is moderately active in NSCLC with brain metastases and is more effective in EGFR mutation positive individuals.[5]

2.1.2 *Gefitinib*

Gefitinib is an EGFR inhibitor and is used for NSCLC.[6] Gefitinib and its CNS penetration was assessed in 15 Japanese patients diagnosed with NSCLC and brain metastases. They were administered 250 mg of gefitinib and 150 mg of erlotinib. The CSF concentration and penetration rate were higher for erlotinib than gefitinib and this led to higher CNS response rates in the erlotinib patients.[7] Similarly, Zhao et al. conducted a study in which 22 patients with lung adenocarcinoma and brain metastases were given gefitinib. They showed that the CSF concentration of gefitinib was low, and correlated with the plasma concentration. Hence, to achieve higher CSF concentration in NSCLC with brain metastases, higher doses of gefitinib should be used.[8]

A prospective trial was undertaken by Ceresoli et al. in which gefitinib was given to NSCLC patients with brain metastases to assess its safety and efficacy. In the 41 patients, 250 mg of gefitinib was administered. 4 (10%) had a partial response, 7 (17%) had a stable disease and the overall disease control rate was 27%. The conclusion was that gefitinib can be active in brain metastases in NSCLC. The standard therapy, prior chemotherapy and whole brain radiation therapy (WBRT), was also assessed and revealed disappointing results. As a result, the study concluded that gefitinib is a new treatment option.[9] Similarly, a meta-analysis of 7 trials looked at erlotinib/gefitinib with WBRT, WBRT alone, or WBRT with chemotherapy. It concluded that erlotinib/gefitinib plus WBRT was superior to WBRT alone, as the overall response rate was 2.16.[10] Additionally, gefitinib's effect was studied in NSCLC patients with brain metastases. Of the 57 patients, 14 had brain metastases, 1 had complete response, 5 had partial responses, and 8 had stable disease in the brain. This study found that in refractory NSCLC, gefitinib has efficacy and is well tolerated.[11]

2.1.3 *Afatinib*

Afatinib is an EGFR inhibitor used for metastatic NSCLC with EGFR exon 19 deletions or exon 21 substitution mutations.[12] Tamiya et al. studied afatinib's CSF penetration rate. The study included 11 patients with EGFR positive advanced NSCLC, who were given afatinib at 40 mg/day. On day 8, the CSF penetration rate was 2.45+/-2.91%. The overall response rate was 27.3%. This study concluded that afatinib was effective for NSCLC with uncommon EGFR mutations.[13] In the two trials, LUX-Lung 3 and LUX-Lung 6, NSCLC with EGFR mutations and brain metastases patients treated with afatinib had improved progression free survival (8.2 vs. 5.4 months) and overall response rate (73% vs. 25%) when compared to standard platinum therapy.[14]

2.1.4 *Osimertinib*

Osimertinib is an EGFR inhibitor that is selective for EGFR-TKI sensitizing and T790M resistance mutations in NSCLC. Soria et al. conducted a study which included 556 patients with previously untreated EGRF mutation-positive (exon 19 deletion or L858R) locally advanced or metastatic NSCLC. They were distributed into three treatment groups. Patients received either 80 mg of osimertinib, or 250 mg of gefitinib, or 150 mg of erlotinib. CNS progression occurred in 17 (6%) patients on osimertinib and 42 (15%) patients who were given the standard EGFR-TKI therapy. All these results stated that osimertinib had a prolonged progression free survival than the current standard EGFR mutation-positive treatment.[15]

2.2 ALK inhibitors

2.2.1 *Crizotinib*

Crizotinib is FDA approved for metastatic NSCLC ALK+ mutations. It binds to ATP in a competitive manner, which results in binding and inhibition of ALK kinase and ALK fusion proteins. It also blocks the c-met pathway. These then cause inhibition of tumor growth. Crizotinib's CSF concentration has been studied by Costa et al. and Metro et al. Their results show that crizotinib has poor CFS concentration, as evidenced by low CSF to serum ratios. However, despite the poor CSF concentration some patients with brain metastases benefited from crizotinib. This finding requires further study to determine the underlying mechanisms. Crizotinib is also a p-glycoprotein substrate. The efficacy of crizotinib was studied in the PROFILE 1014 trial, in which crizotinib was compared to standard chemotherapy (platinum doublets). The results showed that intracranial disease control rate was 56% vs. 25% respectively.[16]

2.2.2 *Ceritinib*

Certinib is used for metastatic NSCLC ALK+ mutations. It is a tyrosine kinase, Cytochrome P450 3A, and Cytochrome

P450 2C9 inhibitor. It binds and blocks ALK kinase, ALK fusion proteins and ALK point mutation variants, and inhibits cell growth in ALK-overexpressing tumor cells. A preclinical rat model demonstrated ceritinib's penetration of the blood brain barrier with a CSF and plasma ratio of 15%. In the ASCEND 3 trial, ceritinib was administered to 50 patients with brain metastases at baseline, 27 of whom had prior radiotherapy. In 17 patients, the intracranial response rate was 58.9% and disease control rate was 82.4%. This study suggests that ceritinib can be active in brain metastases, especially in those who have not had any prior treatment with ALK inhibitors.[16]

2.2.3 *Alectinib*

Alectinib is an ALK inhibitor which is used for NSCLC with ALK+ mutations. Alectinib has a potent antineoplastic activity against intracranial lesions due to its high rate of CNS penetration. It is not a substrate for p-glycoprotein and hence is not effluxed. The efficacy of alectinib was assessed in several trials. In the AF-002JG study, of 21 patients with brain metastases, 6 (29%) had complete response, 5 (24%) had partial response, 8 (38%) had stable disease and 2 (10%) had progressive disease. Similarly, the NP28761 trail showed a response rate of 68.8% and disease control rate was 100% in patients with baseline intracranial lesions treated with alectinib.[16]

2.3 VEGF inhibitor

Bevacizumab

Bevacizumab is a recombinant human neutralizing VEGF IgG antibody, which inhibits tumor angiogenesis. It is FDA approved for NSCLC. Bevacizumab acts on intracranial lesions, not by disrupting the blood brain barrier, but through neutralizing the VEGF within the lumen of capillaries. The efficacy of bevacizumab was assessed in the BRAIN study. In the trial, NSCLC patients with asymptomatic brain metastases were divided into two arms: Arm #1 - bevacizumab, paclitaxel, and carboplatin; Arm #2 - bevacizumab and erlotinib. The response rates for the intracranial and extracranial metastases in both arms were identical. Bevacizumab had an acceptable safety profile in this patient population.[17]

3. MELANOMA

Targeted therapies that are used in melanoma act on the mitogen-activated protein (MAP) kinase pathway. In this pathway, RAS protein is activated, which then stimulates the RAF kinases ARAF, BRAF and RAF1. These kinases then cause MEK kinase phosphorylation that activates ERK kinase. This controls cyclin D1, which causes cellular division and progression.[18] The targeted therapies available for the treatment of melanoma are BRAF inhibitors, MEK inhibitors, and immunotherapy.

3.1 BRAF inhibitors

3.1.1 *Vemurafenib*

Vemurafenib is a BRAF inhibitor which is used for unresectable or metastatic melanoma with BRAF (V600) mutations. According to Mittapalli et al. vemurafenib is effluxed by p-glycoprotein and BCRP, which constitute the blood brain barrier. Vemurafenib's CNS distribution is severely restricted.[19] However, in a phase 2 clinical trial by McArthur et al., 146 metastatic melanoma patients were given vemurafenib. They were distributed in two cohorts, (1) previously untreated brain metastases and (2) previously treated brain metastases. In cohort 1, the intracranial best overall response rate was 18%. The study authors concluded that vemurafenib use in melanoma with brain metastases has a clinically meaningful response rate.[20] In another study by Dummer et al. vemurafenib was used for BRAF (V600) mutation-positive melanoma patients with symptomatic brain metastases. For intracranial and extracranial sites, an overall partial response was reached in 10 out of 24 patients (42%). Out of the 19 patients with measurable intracranial disease, 7 (37%) had intracranial tumor regression, and 3 (16%) had a partial response.[21]

3.1.2 *Dabrafenib*

Dabrafenib is a BRAF protein inhibitor that decreases cellular proliferation of tumor cells containing a mutated BRAF gene. In a phase 1 dose escalation trial, patients with melanoma and untreated brain metastases were included. 9 out of 10 had reductions in the size of their brain lesions.[22] Even with the response seen in this trial, the CNS distribution of dabrafenib was uncertain. Mittapalli et al. looked at the CNS penetration of dabrafenib. The results showed that dabrafenib is a substrate for p-glycoprotein and BCRP, which efflux dabrafenib. Hence, dabrafenib has limited CNS penetration. However, the study also compared the CNS distribution of vemurafenib to dabrafenib and found that dabrafenib had greater CNS penetration at a similar dose.[23] Thus, dabrafenib appears to be a better option than vemurafenib. In a study by Rodgers et al. the CNS penetration of dabrafenib was evaluated. They concluded that there were quantifiable concentrations of dabrafenib in the plasma, but CSF had low concentrations.[24]

In the BREAK-MB, multicenter phase 2 trial, dabrafenib's safety and efficacy were assessed in 172 patients with BRAF V600E, V600K mutations and metastatic melanoma with at least one measurable brain metastasis. They were divided into two cohorts, (A) no local therapy and (B) with progression after local therapy. The results showed that the overall intracranial objective response in cohort A was 39% and in cohort B was 31%. As BRAF inhibitors have a high rate of intracranial objective response, they should be considered in BRAF mutated melanoma.[1]

Table 1. CNS distribution and Efficacy of Targeted Therapies in Advanced NSCLC

Targeted therapy	Mechanism of action	CNS penetration	Clinical trials	Results of clinical trials
Erlotinib	EGFR inhibitor	-at a dose of 150 mg, CSF concentration 5.1% -as plasma concentration increases, CSF concentration increases	-Bai et al.	-out of 40 patients: Partial response -4 Stable disease-21 Progressive disease-15
Gefitinib	EGFR inhibitor	-CSF concentration is low -as plasma concentration increases, CSF concentration increases	-Ceresoli et al. -Meta-analysis by Zheng et al. -Hotta et al.	-out of 41 patients: Partial response-4 Stable disease-7 Overall disease control rate-27% -gefitinib/erlotinib plus WBRT superior to WBRT alone -overall response rate 2.16 -out of 14 patients with brain metastases: Complete response-1 Partial response-5 Stable disease-8
Afatinib	EGFR inhibitor -exon 19 deletions -exon 21 substitutions	-at a dose of 40 mg/day, CSF penetration rate was 2.45+/-2.91%, with overall response rate of 27.3%	-LUX-Lung 3 and LUX-Lung 6 trials	-overall response rate of 73%
Osimertinib	EGFR inhibitor	-N/A	-Soria et al.	-CNS progression occurred in 17 (6%) osimertinib and 42 (15%) in standard EGFR-TKI group.
Crizotinib	ALK inhibitor	-low CSF to serum ratios -poor CSF concentration -p-glycoprotein substrate	-PROFILE 1014	-disease control rate of 56%
Certinib	ALK inhibitor	-penetrated the blood brain barrier at a ratio of 15%	-ASCEND 3	-out of 50 patients: Overall response rate-58.9% Disease control rate-82.4%
Alectinib	ALK inhibitor	-high rate of CNS penetration -not a substrate for p-glycoprotein	-AF-002JG -NP28761	-out of 21 patients: Complete response-6 Partial response-5 Stable disease-8 Progressive disease-2 -response rate-68.8% -disease control rate-100%
Bevacizumab	VEGF inhibitor	-does not disrupt the blood brain barrier -acts on VEGF	-BRAIN -compared bevacizumab, carboplatin, paclitaxel to bevacizumab, erlotinib	-response rates for intracranial and extracranial sites were identical in the two arms
Nivolumab	PD1 inhibitor	-targets intracranial metastasis through pre-existing tumor infiltrating lymphocytes	-Borghaei et al.	-overall survival at 1 year-51%
Pembrolizumab	PD1 inhibitor	-targets intracranial metastasis through pre-existing tumor infiltrating lymphocytes	-Langer el al.	-out of 123 patients: -pembrolzumab, carboplatin and premetrexed group objective response: 33 -chemotherapy group objective response: 18

Table 2. CNS distribution and Efficacy of Targeted Therapies in Advanced Melanoma

Targeted therapy	Mechanism of action	CNS penetration	Clinical trials	Results of clinical trials
Vemurafenib	BRAF inhibitor	-effluxed by p-glycoprotein and BCRP -CNS distribution severely restricted	-McArthur et al. -Dummer et al.	-intracranial best overall response rate 18% in patients who had untreated brain metastases -out of 19 patients with measurable intracranial lesions, 7 had tumor regression, 3 partial response
Dabrafenib	BRAF inhibitor	-effluxed by p-glycoprotein and BCRP -darafebnib greater penetration into the brain than vemurafenib at a similar dose	-BREAK-MB, two cohorts Cohort A: no local therapy Cohort B: progression after local therapy	-overall intracranial objective response: Cohort A: 39% Cohort B: 31%
Trametinib	MEK inhibitor	-restricted brain distribution -substrate of p-glycoprotein and BCRP	-Robert et al. -darafenib and trametinib compared to vemurafenib alone	-improved overall survival in the combined group -objective response rate: Dabrafenib and trametinib: 64% Vemurafenib: 51%
Ipilimumab	Monoclonal antibody against CTLA4	-acts against brain metastases through activated T cells	-Margolin et al. Cohort A: no steroids, asymptomatic Cohort B: steroids and symptomatic -Hodi et al.	-ipilimumab used in both cohorts: Disease control in cohort A – 12 Disease control in cohort B – 2 -ipilimumab with gp100 vaccine had improved overall survival (10.1 months)
Nivolumab	PD1 inhibitor	-targets intracranial metastasis through pre-existing tumor infiltrating lymphocytes	-Cohen et al. -Borghaei et al.	-groups with nivolumab showed statistically significant progression free survival than ipilimumab -nivolumab has overall survival at 1 year of 51% compared with docetaxel at 39%
Pembrolizumab	PD1 inhibitor	-targets intracranial metastasis through pre-existing tumor infiltrating lymphocytes	-Robert et al.	-pembrolizumab prolonged progression free survival and overall survival than ipilimubmab

3.2 MEK inhibitor

Trametinib

Trametinib is a MEK inhibitor used with dabrafenib for unresectable or metastatic melanoma with BRAF (V600E or V600K) mutations. As there is emerging resistance encountered downstream to BRAF in the MAPK signaling pathway, trametinib offers a novel way to overcome this resistance by acting through MEK-1/2. Hence, concurrent therapy with a BRAF inhibitor and trametinib is preferred. In a phase 3 trial in which trametinib was combined with dabrafenib, there was improved overall survival in untreated metastatic melanoma with BRAF V600E or V600K mutations.[25] Trametinib's CNS penetration was evaluated by Vaidhyanathan et al. in which they concluded that trametinib has a restricted brain distribution as it is a p-glycoprotein and BCRP substrate.[26]

3.3 Immunotherapy

Ipilimumab is a humanized monoclonal anti-CTLA4 (cytotoxic T lymphocyte antigen-4) used for the treatment of unresectable or metastatic melanoma.[1] Ipilimumab does not have a good CNS penetration because of its molecular size. It acts against the brain metastases through activated T-cells.[27] In a phase III trial, ipilimumab, with or without a gp100 peptide vaccine, compared to gp100 peptide alone, showed an improved overall survival (10.1 months) for previously treated metastatic melanoma.[28] In a phase 2 trial, 72 patients with melanoma and brain metastases were divided into two cohorts, A - neurologically asymptomatic with no corticosteroids, B - symptomatic with corticosteroids. Ipilimumab was administered in both cohorts. Disease control in the brain was shown in 12 (24%) in cohort A and 2 (10%) in cohort B (10%). The trial authors concluded that ipili-

mumab had some activity in advanced melanoma with brain metastases.[27]

4. Melanoma and NSCLC

4.1 PD1/PDL1 inhibitors

In the human body, the peptide fragments on the antigen presenting cells are recognized by the T cells, which in turn activate cellular immunity. This T cell stimulation is usually deactivated by a pathway that consists of programmed cell death receptor 1 (PD-1). When PD1 binds with PDL1, which is on tumor cells, it downregulates the T cells ability to mount a response against tumor cells. PD1 and PDL1 antibodies, such as nivolumab and pembrolizumab, restore the antitumor response in patients with melanoma.[29] It is hypothesized that there might be tumor infiltrating lymphocytes, and immune modulation by these agents allows cytotoxic T cells migration into the brain.[30]

4.1.1 *Nivolumab*

Nivolumab is used for metastatic melanoma and chemotherapy resistant metastatic NSCLC. In a multicenter, randomized trial, 945 patients with prior untreated, unresectable, or metastatic melanoma were divided into three groups; nivolumab with ipilimumab, nivolumab, and ipilimumab. The study concluded that progression free survival was statistically significant in the nivolumab groups than ipilimumab alone.[31] Nivolumab is FDA approved as a monotherapy or in combination with ipilimumab in unresectable or metastatic melanoma. In a phase 3 trial, nivolumab was compared to docetaxel in advanced NSCLC patents. The overall survival at 1 year with nivolumab was 51% and for docetaxel was 39%.[32]

4.1.2 *Pembrolizumab*

Pembrolizumab is FDA approved for unresectable or metastatic melanoma. A phase 3 trial showed that pembrolizumab demonstrated a longer progression free survival and overall survival compared to ipilimumab.[33] Pembrolizumab is also approved as a first line agent for metastatic NSCLC with expression of PDL1 on at least 50% of tumor cells, and as second line agent for metastatic NSCLC after platinum based chemotherapy is ineffective in controlling progression. Based on a phase 2 clinical trial of 123 patients, carboplatin and pemetrexed pembrolizumab with/without in advanced NSCLC concluded that an objective response was achieved in 33 with pembrolizumab and 18 with chemotherapy. The study concluded that pembrolizumab, carboplatin and pemetrexed combination is effective and well tolerated.[34]

5. Conclusion

The various targeted therapies reviewed in this paper have shown activity against brain metastases in NSCLC and melanoma patients (see Tables 1 and 2). Most of the targeted therapies have a low CNS penetration, however in clinical trials they have proven to be clinically effective. The targeted therapies provide newer treatment options for an advanced stage disease, when compared to surgery, stereotactic radiotherapy or chemotherapy. By utilizing the information about the CNS distribution and efficacy of the targeted therapies, clinicians could tailor a management plan for patients with metastatic NSCLC and melanoma. To further our understanding about the efficacy of targeted therapies, clinical trials should be conducted to evaluate targeted therapies as first-line treatment options for patients with NSCLC and melanoma with brain metastases. Through specific research about the targeted therapies, we would be able to highlight their effectiveness as well as their associated adverse effects and outcomes, which would aid in the decision-making process.

Conflicts of Interest Disclosure

The authors declare that there is no conflict of interest statement.

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