Review Article

Are immune checkpoint blockade monoclonal antibodies active against CNS metastases from NSCLC?—current evidence and future perspectives

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Abstract: Brain metastases occur in approximately half of patients with non-small cell lung cancer (NSCLC) and are associated with a poor prognosis and an inferior quality of life. Historically systemic therapy has had a limited role in CNS disease with a reliance placed on local treatments. The emergence of targeted therapies and immune checkpoint inhibitors (ICIs) in recent years has dramatically changed the treatment landscape of NSCLC. Programmed cell death-1 (PD-1) inhibitors have demonstrated efficacy in three randomized trials and now represent standard second line therapy after platinum failure. Trials have largely excluded patients with symptomatic or untreated CNS disease as the brain has been considered an 'immune-privileged' organ. We review the evidence and future prospects of ICIs in treating brain metastases in NSCLC.

Keywords: Brain metastases; immune checkpoint inhibitors (ICIs); non-small cell lung cancer (NSCLC)

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Introduction

Lung cancer remains the leading cause of cancer mortality in men and women worldwide (1). Non-small cell lung cancer (NSCLC) is the most common subtype accounting for approximately 85% of all lung cancers (2). The 5-year survival in unselected NSCLC at all stages of diagnosis remains less than 20% and for stage IV disease is less than 5% (3,4). In advanced NSCLC, testing for distinct molecular genotypes has led to a personalized approach to treatment, which has improved outcomes when compared to standard platinum chemotherapy (5-13). Maintenance chemotherapy and other targeted agents have had a modest impact on survival (14-16). Immune checkpoint inhibitors (ICIs) are negative regulators of T cells and include anti cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibodies and anti-programmed cell death-1 (anti-PD-1)/programmed cell death receptor ligand-1 (PD-L1) antibodies. These drugs have demonstrated efficacy in NSCLC, melanoma and renal cell cancer, three cancer types with a predilection to brain metastases. Approximately 30–50% of patients with NSCLC can expect to develop CNS disease at some point (17,18). The number of patients with brain metastases is rising and can be explained by the more frequent use of sensitive imaging techniques such as magnetic resonance incidence (MRI) and by the improved survival seen in patients owing to new systemic treatments (19,20). Patients with molecular subtypes such as epidermal growth factor receptor positive (*EGFR*+) and anaplastic lymphoma kinase positive (*ALK*+) lung cancers may have an increased risk of CNS disease at diagnosis compared with *EGFR/ALK* wild-type (WT) NSCLC however this risk may also be explained by a potential lag in diagnosis in this patient population (21-23). The overall survival (OS) in patients with brain metastases is variable and ranges from 3 to 15 months (24). Prognostic

factors such as number of lesions, performance status and extra-cranial control are important determinants (24). In the *EGFR*+ and *ALK*+ subgroups a superior survival of 34 and 38 months respectively has been reported (25).

Historically standard treatments for brain metastases in NSCLC focused on achieving local control with mixed results. Dependent on size, number, symptoms, site and histology of lesions, patients may have been offered surgery and or whole brain radiation (WBRT). WBRT is associated with cognitive decline and inferior quality of life (26-28). While stereotactic radiosurgery (SRS) has the advantage of less cognitive impairment and shorter treatment times, the number of metastases is thought to limit SRS (28). Systemic treatment has inferior CNS disease control due to variable penetration across the blood brain barrier (BBB) (29). Platinum regimens have however demonstrated response rates between 23–50%, which approximated extra-cranial responses (30). Guidelines have suggested that chemotherapy could have a role in patients with asymptomatic disease where local therapies are not possible (31). Bevacizumab in combination with carboplatin/paclitaxel has demonstrated efficacy and early results of a phase II study of 67 patients with non-squamous histology and brain metastases, revealed a 61.2% overall response rate (ORR) in intracranial lesions and a 6-month progression-free survival (PFS) of 56.5% (32). Oral *EGFR*-tyrosine kinase inhibitors (TKIs) and *ALK* inhibitors can gain access to the CNS and response rates, especially in *ALK*+ NSCLC are promising (33-38).

ICIs in NSCLC

The evasion of immune destruction is now recognized as a hallmark of cancer (39). Immune checkpoints are crucial to this and under normal physiological conditions control immune homeostasis and prevent autoimmunity (40). Immune checkpoints belong to a large diverse family of receptors that can negatively impact the efferent immune response by impairing T cell clonal expansion, repressing function and activation and by preventing immune attack against tumor antigens (41). The PD-1/PD-L1 and CTLA-4 axes are the most common checkpoints studied with monoclonal antibodies that can inhibit ligand binding. CTLA-4 is expressed on T cells and appears to primarily inhibit the early activation of effector T cells within lymphoid organs and can enhance the immunosuppressive FOXP3+ regulatory T (Treg) cell population (42). PD-1 counterattacks the T cell response foremost at the tumor or inflammatory site and is upregulated on activated T-cells and other immune cells within the tumor microenvironment. Binding of PD-1 to its ligands (PD-L1 and PD-L2) promotes tumor immune escape by initiating a signaling cascade that inhibits T cell proliferation and limits cytotoxic function (41,43). PD-L1 can be found on a spectrum of cells including endothelial and epithelial cells together with T and B cells, mast and dendritic cells and the high expression of PD-L1 in NSCLC may correlate with inferior prognosis (44). Nivolumab and pembrolizumab are IgG4 monoclonal antibodies targeting PD-1 with early efficacy data presented in phase I studies (45,46). Three large randomized trials have recently confirmed the activity and improved survival of PD-1 inhibitors after failure of first line platinum chemotherapy in unselected NSCLC as well as those selected by tumor PD-L1 expression (47-49). Durable responses across trials are reported in approximately 20% of patients, 30% of those with PD-L1 tumor expression (45,48-50). PD-1 inhibitors now represent a standard option in NSCLC patients with metastatic disease. The efficacy of PD-L1 inhibitors post platinum doublet chemotherapy (POPLAR) and the combination of CTLA-4 inhibitors and PD-L1 inhibitors has also been established (51,52). Trials comparing ICIs to chemotherapy in the first-line setting are expected to report in 2016, with ongoing trials of combination ICI plus chemotherapy regimens versus standard first-line chemotherapy (53,54). The only biomarker known to predict response to PD-1 axis inhibitors in NSCLC is the percentage of PD-L1 positive tumor cells. In KEYNOTE-010, untreated patients who had a tumor proportion score ≥50% (membranous PD-L1 expression in at least 50% of tumor cells) demonstrated higher response rates of 50% (47). This is however far from an ideal biomarker and the lack of PD-L1 expression does not preclude a response (48,49,53,55,56). There has been a growing interest in mutation load as a predictive marker for immune checkpoint inhibition; determining this however, may be costly and impractical on a global scale (57,58). Most of the published studies of ICIs in NSCLC required local CNS control and stability prior to study entry, thus the value of ICIs in patients with brain metastases is understudied.

The immunogenicity of the CNS

Until recently the brain was considered an immune-privileged organ, a term first coined by Billingham and Boswell in the 1950s (59,60). The limited regenerative capacity of neural cells means that strict control must be

in place to prevent autoimmunity. Over the past century foreign tissues and pathogens have been shown to evade the immune system when transplanted into brain parenchyma (61-63). Anatomical barriers such as the BBB and an absent lymphatic system were thought responsible for poor CNS immunogenicity. The latter has now been refuted since the discovery of an intact CNS lymphatic system, which questions our traditional understanding of CSF flow and explains how peripheral immune responses can be generated (64,65). CNS-specific immune cells have also been shown to traverse the cribriform plate in order to reach deep cervical nodes (66). Although the BBB restricts access and flow of peripheral innate and adaptive immune cells, other interfaces such as the CSF and choroid plexus can provide mechanisms of entry (67).

The various compartments of the CNS are complex and heterogeneous in immune cell composition. Microglia are the only immune cells within brain parenchyma and are considered poor antigen presenting cells (68). However within the ventricles, leptomeninges and perivascular spaces are cells of the innate immune system, predominantly macrophages, as well as of the adaptive immune system with a relatively high density of CD4+ memory T cells (67,69). These resident cells are important for ongoing immunesurveillance. Once the CNS becomes inflamed or tumourigenesis initiates, the BBB becomes more permeable and the production of cytokines and chemokines may perpetuate immune cell infiltration (60). Despite this theory, primary CNS tumors do not appear to have a high density of tumor infiltrating lymphocytes (TILs) whereas renal cell carcinomas and melanomas have a higher TIL burden in the microenvironment in CNS metastases (70,71). Similar to systemic disease, the reasons for immune cell heterogeneity within the tumor environment have not been fully explained.

A number of studies have evaluated the prognostic impact of TILs in systemic cancers (72). Within the CNS, the association of TILs with survival has been conflicting. Harter *et al*. investigated a large cohort of patients with CNS tumors including NSCLC metastasis (n=62) and could not find a correlation between TIL burden and patient survival. This group also reported low TIL levels in lung cancer brain metastases, with highest density of TILs in RCC and melanoma (73). Similarly Berghoff reported increased TILs in RCC and melanoma brain metastases but also reported high density in NSCLC samples (n=57), and correlated survival with density of TILs and the 'immunoscore' (71). Both studies were retrospective and the latter only included patients with a single brain metastasis. The median number of lesions in the study by Harter *et al*. was also one. Lung cancer genotype was not available in either study.

An analysis of PD-L1 and TIL densities in NSCLC primary tumor and matched brain metastases revealed higher PD-L1 expression in brain metastases (52% *vs*. 32%) but denser TILs in primary tumors (74). The density of TILs in tumor may be a predictive marker for immune checkpoint inhibition. Given that the non-synonymous mutational burden may represent a predictive marker in NSCLC, the differences in mutational load in systemic disease versus brain metastases may be a contributing factor in TIL differences but this theory has not been explored (57).

Immunotherapy in NSCLC CNS disease—clinical evidence

Clinical evidence to support the efficacy of ICIs in CNS disease is limited. Early data from a phase II study has been reported by Goldberg *et al*. and represents the first report of PD-1 inhibitors in untreated or progressive NSCLC brain metastases (75). This single institution study enrolled 18 patients with melanoma and 18 patients with NSCLC including one *EGFR*+ and one *ALK*+ lung cancer patient. Patients were required to have asymptomatic intracranial disease with at least one brain metastasis measuring between 5 and 20 mm that was untreated. Primary NSCLC tumors had to have at least 1% PD-L1 staining. In the lung group, 10/18 patients had received previous local therapy for brain metastases but evidence of progressive disease. All patients received pembrolizumab 10 mg/kg every 2 weeks until disease progression. Among the patients with NSCLC, 33% of patients (n=6) had a response (four with complete response, one each with confirmed and unconfirmed partial response) with a median response duration of more than 6 months. The numbers of CNS responders in both cohorts correlated with patients achieving a systemic response. Responses in the CNS lasted from 3 to 7 months. It is unknown if responders included specific molecular subtypes. Another third (n=6) of NSCLC patients had confirmed progressive disease intra-cranially and an additional four (22%) could not be evaluated due to rapid systemic progression. The median OS in the NSCLC cohort was 7.7 months but had not been reached in the melanoma group. Neurological toxicities were predominantly grade 1–2, such as seizures, headache and dizziness, and did not result in treatment cessation. Cognitive dysfunction and stroke were less common although a melanoma patient experienced a

Table 1 Ongoing studies including untreated brain metastases in NSCLC

Group or institution trial	Phase	Study	Status
Yale University, NCT02681549	II	Pembrolizumab plus bevacizumab for treatment of brain metastases in metastatic melanoma or NSCLC	Recruiting
BMS, CheckMate 012	I	Study of nivolumab (BMS-936558) in combination with gemcitabine/cisplatin, pemetrexed/cisplatin, carboplatin/paclitaxel, bevacizumab maintenance, erlotinib, ipilimumab or as monotherapy in subjects with stage IIIB/IV NSCLC (CheckMate 012)	Ongoing but not accruing
MD Anderson, NCT02444741	I/II	MK-3475 and hypofractionated stereotactic radiation therapy in patients with NSCLC	Recruiting
Medimmune, D4190C00006	I	A phase Ib study of MEDI4736 in combination with tremelimumab in subjects with advanced NSCLC (52)	Recruiting
AstraZeneca, NCT02179671	II	Immune-modulated study of selected small molecules (gefitinib, AZD9291, or selumetinib + docetaxel) or a 1st immune-mediated therapy (IMT; tremelimumab) with a sequential switch to a 2nd IMT (MEDI4736) in patients with locally advanced or metastatic non-small-cell lung cancer	Completed

NSCLC, non-small cell lung cancer.

transient but severe episode of cognitive dysfunction.

In a phase II study (CheckMate 063) of nivolumab, lung cancer patients with squamous cell cancer who had received at least two lines of systemic treatment were treated with nivolumab. Of two patients with evaluable CNS disease, both had a response (55). Neurotoxicity was again uncommon. A further retrospective review of five patients with NSCLC and new or progressing brain metastases not requiring corticosteroids were treated with nivolumab. Two patients had an intracranial response, including one partial response and one complete response both sustained for over 24 weeks (76). A number of early phase immunotherapy trials are now including patients with untreated asymptomatic CNS disease; however as yet there are no phase III studies that allow enrolment of patients with untreated brain metastases from NSCLC (*Table 1*).

In patients with brain metastases from melanoma, the role of ICIs has been more extensively investigated. Ipilimumab, a CTLA-4 inhibitor, was evaluated in both patients with asymptomatic brain metastases and those with symptomatic disease requiring steroids. The response rates were 18% and 5% respectively (77). It should be noted that 76% of patients with asymptomatic disease had progressive brain metastases at 12 weeks, likely requiring local interventions (78). A retrospective study of ipilimumab reported similar responses (79).

Updated analysis from a phase II study of ipilimumab and fotemustine in metastatic melanoma (NIBIT-M1) has confirmed that 7 of 20 patients enrolled with brain metastases were alive over 2 years from study entry (80). The NIBIT 3 phase III study includes a cohort of patients with untreated asymptomatic brain metastases (81).

Nivolumab has also demonstrated activity in hypermutated glioblastoma and may have a role in primary neurodegenerative disorders such as Alzheimer's disease which reinforces the potential application of ICIs in select populations with intracranial pathology (58,82).

While limited data suggest that intracranial response rates to ICIs are similar to response rates with platinum doublet therapy, ICI therapy has the distinct advantage of producing durable responses in select patients. As yet there is no definitive biomarker to enrich this population. The role of ICIs in *EGFR*+ and *ALK*+ NSCLC has been controversial, with subgroup analyses of phase III trials suggesting no significant survival advantage over second-line chemotherapy (47,48). Gettinger *et al*. on the other hand did report responses in *EGFR*+ patients and a recent study has shown that *EGFR/ALK*+ lung cancer may upregulate PD-L1 expression through activation of PI3K-AKT and MEK-ERK signaling pathways (53,83). In these molecular subgroups where the incidence of brain metastases is high, further clarification of response to ICIs will be important. When brain metastases develop, the cost of patient care rises significantly (84). It is unlikely that use of ICIs without better patient selection will be cost effective in treating an overall poor prognostic cohort of patients.

Future prospects

A number of studies are now investigating the role of

ICIs in patients with untreated brain metastases and it is likely that this will expand following the recent report of Goldberg and colleagues. For example, CheckMate 012, a phase I study of combination nivolumab and ipilimumab in NSCLC, includes an arm of patients with asymptomatic brain metastases (*Table 1*). The role of combination radiation and immunotherapy is a rapidly evolving field. Specifically in the brain metastases population, combinations of ipilimumab/SRS and nivolumab/SRS have demonstrated safety and feasibility in retrospective analyses of melanoma patients (85-87). Kniesley reported a series of melanoma patients with brain metastases and found an improvement in median survival of 21.3 *vs*. 4.9 months when ipilimumab was added to SRS. Radiation necrosis is however, thought to occur with a higher frequency when immunotherapy is used (88). Also the potential for an abscopal effect in malignancy is a subject of great interest, with case reports in NSCLC (89,90). Radiation is thought to repair aberrant vasculature and attract tumor specific T cells into the tumor microenvironment therefore enhancing the immune response (91). Recently it has been shown in mouse models that there is a persistent influx of bone marrow-derived immune cells into the CNS after radiation, suggesting that the physiologic effects of radiation may unleash restraints on the regulation of immune homeostasis (92). The diagnosis of pseudoprogression can be a challenge and case reports of surgical resections have revealed necrotic tissue with inflammatory cells and only scattered tumor cells (93,94).

Given that patients with small asymptomatic brain lesions seem to respond best to ICIs, and that brain metastases have a lower TIL infiltrate compared to primary lung tumors, immunotherapy in the adjuvant setting may be more efficacious in delaying time to development of CNS disease. The adjuvant studies of immunotherapy versus placebo post resection or radical chemoradiation in stage III disease (NCT02273375, NCT02595944, NCT02125461) will help address this question.

Conclusions

A select group of patients with brain metastases from NSCLC may have durable responses to immune checkpoint blockade. More data are needed for better patient selection but this cohort is likely to reflect extra-cranial responders. Combination treatments including radiotherapy may enhance outcomes. In a historically poor prognostic patient population, ICIs offer a promising systemic approach to intracranial disease without major toxicity.

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Footnote

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