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Review

Systemic therapy in patients with NSCLC with brain metastasis: the emerging role of immunotherapy

Jiaxin Niu[1], Junle Zhou[2], Sara Lindebak[1], Fade Mahmoud[1]

[1]Department of Medical Oncology, Banner MD Anderson Cancer Center, Gilbert, AZ 85234, USA.
[2]Department of Pharmacy, Banner MD Anderson Cancer Center, Gilbert, AZ 85234, USA.

Correspondence to: Dr. Jiaxin Niu, Department of Medical Oncology, Banner MD Anderson Cancer Center, 2946 E Banner Gateway Dr., Gilbert, AZ 85234, USA. E-mail: jiaxin.niu@bannerhealth.com

ABSTRACT

Brain metastasis (BM) is very common in advanced non-small cell lung cancer (NSCLC) patients. The development of BM remains a serious complication associated with significant morbidity and mortality. The traditional approach has been largely focusing on local therapy with surgery and/or radiation. New approaches to treat BM in NSCLC are urgently needed to offer safe and effective therapy as well as to preserve neurocognitive function. There has been significant progress in development of systemic therapies to treat advanced NSCLC in recent years. Targeted therapy has been gradually incorporated into clinical practice to manage NSCLC with BM. Immunotherapy (IO) has revolutionized our treatment paradigm to manage advanced NSCLC. In this review we outline the systemic options for NSCLC-related BM and discuss IO in NSCLC. Finally, we describe the available data and future perspective to support the use of IO in NSCLC patients with BM.

Keywords: Immunotherapy, non-small cell lung cancer, brain metastasis

INTRODUCTION

An estimated 1.8 million new lung cancer cases occurred worldwide in 2012, accounting for approximately 13% of total cancer diagnoses. Lung cancer is the leading cause of cancer mortality in both men and women in developed countries[1]. Roughly 85% of lung cancers are non-small cell lung cancer (NSCLC) and the 5-year survival rate in stage IV remains less than 5%[2]. Brain metastasis (BM) has long been recognized to represent a common event in NSCLC. About 10%-25% of NSCLC patients present with BM upon the initial

diagnosis, and up to 50% will develop BM at some point during the course of the disease[3,4]. The incidence of BM appears to have increased in the past decade due to the wide use of magnetic resonance imaging to detect smaller lesions as well as to the evolution of more effective systemic therapy leading to better control of extra-cranial disease and prolonged survival[5,6]. Historically, the development of BM is associated with poor prognosis with median overall survival (OS) ranging from 3.4 to 7.1 months after whole brain radiation therapy (WBRT)[7].

LOCAL THERAPY

Local therapy with surgery and/or radiation therapy has been the mainstay of treatment for decades. For younger patients with a newly diagnosed solitary BM, surgical resection followed by WBRT is supported by level I evidence and incorporated in some clinical guidelines[8]. WBRT has been the standard of care for NSCLC patients with multiple BM. This practice was recently called into question. In the QUARTZ trial, WBRT failed to show any survival or quality of life benefit compared with steroid and best supportive care in NSCLC patients with multiple BM, although majority of the patients had poor performance status (PS)[9]. On the other hand, WBRT was deemed inadequate in the long-term control of BM in patients with good PS and prolonged survival due to effective systemic therapy. Moreover, these patients may survive long enough to experience significant neurocognitive sequelae associated with WBRT. To avoid neurotoxicity from WBRT, stereotactic radiosurgery (SRS) has been advocated in patients with better prognosis and a limited number of BM. A meta-analysis demonstrated that WBRT with or without SRS did not improve OS compared with SRS alone in patients with up to four BM; whereas SRS was substantially superior in preserving PS and neurocognitive function[10]. A Japanese study of SRS alone for patients with one to ten BM showed that distant brain failure rate and survival did not differ significantly in patients with two to four versus five to ten lesions[11]. In patients with BM who underwent resection, SRS to the surgical cavity was compared head-to-head with WBRT in a randomized phase 3 study. It demonstrated no difference in OS, but less frequent decline in cognitive function (52% *vs.* 85% at 6 months) in SRS group. Thus, SRS is regarded as one of the standards of care after resection of a brain metastasis[12]. For appropriate patients, SRS has been getting increasingly utilized in practice in recent years.

CHEMOTHERAPY

For years the role of systemic therapy in treating BM in NSCLC patients has been neglected owing to the prevailing belief that therapeutic drugs cannot cross the blood brain barrier. Traditional chemotherapy with platinum-based doublets has been shown in the first-line setting to be active in controlling BM in small studies. The commonly used regimens for adenocarcinoma of a platinum plus pemetrexed were shown in phase 2 studies to demonstrate roughly 40% intracranial response rate (ICRR), comparable to systemic response rate[13,14].

TARGET THERAPY

With recent advances in understanding NSCLC biology, many highly specific target agents have become available, redefining the role of systemic therapy in treating BM in NSCLC. In recent years, several distinct molecular driver mutations have been discovered, and the list is getting longer over time. The most common epidermal growth factor receptor (EGFR) mutation constitutes 10%-15% of lung adenocarcinoma in the Western population[15]. Early-generation tyrosine kinase inhibitors (TKIs) have poor penetration to the brain, although they were shown to have variable success in treating BM in a pool analysis[16]. Weekly intermittent "pulsatile" administration of high-dose erlotinib (1500 mg/week) in a small retrospective analysis of 9 patients exhibited an ICRR of 67%, with median time to progression of merely 2.7 months[17]. The 3rd-generation TKI represented by osimertinib, was designed to overcome resistant EGFR mutation T790M and was found to have better permeability in brain. In a pooled analysis of two phase 2 trials, 50 patients with

T790M positive NSCLC with BM were treated with 80 mg osimertinib. The ICRR was 54% (12% CR) and the brain disease control rate (DCR) was 92%; 75% of patients were still in response at 9-month follow-up[18]. Osimertinib showed very impressive PFS as well as intracranial control over gefitinib or erlotinib in newly diagnosed NSCLC with EGFR mutation and has been approved for first-line use[19].

Anaplastic lymphoma kinase (ALK) rearrangement defines another subset of mutations in 3%-5% of NSCLC. BM has been reported in 24% of patients upon diagnosis and up to 70% during the course of disease[20,21]. It is not entirely clear that it is due to poor brain penetration of first-generation TKI, crizotinib, or that the brain is the preferential site of metastasis of ALK + NSCLC. Second-generation ALK TKIs such as ceritinib, brigatinib and alectinib all showed much better brain penetration and great activity against BM. In ALEX trial, a subset of ALK+ NSCLC patients with measurable CNS lesions at baseline were treated with alectinib *vs*. crizotinib. The ICRR and PFS were 81%, 50% and 17.3 months, 5.5 months, respectively[22]. Moreover, 45% of the patients with BM (measurable or nonmeasurable) treated with alectinib achieved CR[22]. Thus, alectinib represents a great treatment option for patients with ALK + NSCLC presenting with BM.

IMMUNOTHERAPY AND NSCLC

Immune checkpoint inhibitors have transformed the treatment paradigm for advanced-stage NSCLC in both frontline and platinum-resistant settings. These agents inhibit a key inhibitory signaling pathway in T cell activation by blocking programmed cell death a (PD-1) from binding to the ligand 1 or 2 (PD-L1/PD-L2), thereby allowing activation of the inactivated T cells[23].

Immunotherapy as first-line treatment

In the pivotal Keynote 024 study, 305 treatment naïve, PD-L1 positive (tumor proportion score, TPS ≥ 50%) patients with advanced-stage NSCLC without EGFR, ALK mutations were randomized to receive pembrolizumab, an anti-PD1 monoclonal antibody *vs*. platinum-based chemotherapy. Pembrolizumab was associated with higher ORR (44.8% *vs*. 27.8%) and prolonged median PFS (10.3 months *vs*. 6.0 months)[24]. Based on this study, the FDA approved the use of pembrolizumab in PDL1 positive patients with advanced-stage NSCLC in frontline setting.

Combinations of immunotherapy with chemotherapy or another immunotherapy agent have also been extensively studied in the past few years. Keynote 189 was another landmark study that confirmed the result of the previously published small phase 2 study on first-line chemo-immunotherapy with carboplatin/pemetrexed/pembrolizumab in previous untreated non-squamous NSCLC patients[25,26]. 616 patients were randomly assigned in a 2:1 ratio, to receive pemetrexed and a platinum-based drug plus either pembrolizumab or placebo every 3 weeks for 4 cycles, followed by pembrolizumab or placebo plus pemetrexed maintenance. The Pembrolizumab–combination group was demonstrated to have a better RR (47.6 % *vs*. 18.9%), a longer PFS (8.8 months *vs*. 4.9 months) and median OS (not reached *vs*. 11.3 months). The benefit was seen in all subgroups, including those with a PD-1 TPS < 1%. The RR was highest in patients with PD-1 TPS ≥ 50% (61.4% *vs*. 22.9%)[26]. Thus, there are two FDA-approved options for NSCLC in the first-line setting at this time. For metastatic squamous NSCLC, platinum/taxane with or without pembrolizumab was investigated in Keynote 407 study. The ORR was 58.4% in the pembrolizumab-chemotherapy group compared with 35% in the chemotherapy group. OS was 15.9 months *vs*. 11.3 months, respectively. PFS was observed in all PD-L1 TPS subgroups, although the PD-L1 high subgroup had a much longer PFS (8 months *vs*. 4.2 months). The platinum/taxane/pembrolizumab combination represents a new standard of care in metastatic squamous NSCLC[27]. Immuno-immunotherapy combination is also under intense investigation. In the Checkmate 227 study, ORR and PFS among patients with a high tumor mutational burden (TMB) defined by at least 10 mutations per megabase was 45.3% and 7.2 months in the immuno-immunotherapy combination group with nivolumab plus ipilimumab irrespective of PD-L1 expression level. The response was more durable, with 68% of patients having an ongoing response after 1 year with combination group *vs*. 25% with chemotherapy[28].

Thus, nivolumab plus ipilimumab may represent a new treatment option in metastatic NSCLC with high TMB, though this combination has not been approved to be used clinically.

Immunotherapy as second-line treatment

Currently there are three agents available in the platinum-resistant setting. Two large phase 3 randomized clinical trials made head-to-head comparison between nivolumab and docetaxel[29,30]. Checkmate 057 included patients with non-squamous histology, and Checkmate 017 included patients with squamous histology with identical trial design[29,30]. Both trials showed superiority of nivolumab in ORR, PFS and OS as well as significant improvement in quality of life[29,30]. Nivolumab was reported to benefit both PD-L1 negative and positive groups with a different antibody, and was approved for 2nd-line use irrespective of PD-L1 expression based on these two trials. Pembrolizumab was compared with docetaxel in the Keynote 010 study wherein it only included PD-L1 positive patients defined as TPS ≥ 1%. The pembrolizumab arm showed significantly better ORR, PFS, OS with a very favorable side effect profile[31]. Thus, pembrolizumab was approved in PD-L1 positive NSCLC after platinum-based first-line therapy. Atezolizumab, a monoclonal antibody against PD-L1, was compared directly with docetaxel in a phase 2 and a phase 3 randomized trial with similar results. Although there was no median PFS advantage in the atezolizumab arm, an OS advantage was found in all subgroups, which led to the addition of atezolizumab to the armamentarium against NSCLC in the second-line setting[32,33]. The landscape of immunotherapy for NSCLC is rapidly changing. These three agents were all approved before first-line immunotherapy became available. With expected wide use of mono-immunotherapy or chemo-immunotherapy combination in the frontline, there is unmet medical need for immunotherapy to overcome immune resistance in previously treated population.

Immunotherapy in NSCLC with brain metastasis

The brain was once believed to be an immune privileged organ to actively suppress any immune response. It is now known that the immune response in brain parenchyma is tightly regulated[34]. In established brain metastases, the tumor microenvironment is composed of the innate immune system, namely microglia and blood-derived myeloid cells/macrophages; and the adaptive immune system, mainly represented by T cells[34,35]. Brain metastases were shown to have higher PDL-1 expression and lower density of tumor in-filtrating lymphocytes (TILs) than the matched NSCLC primary tumors[36]. The immunogenicity of the primary tumor probably influences the T cell response in brain metastases as denser TILs were observed in melanoma-derived brain metastases followed by renal cell carcinoma and NSCLC[37]. The density of TILs seems to correlate well with extent of brain edema and OS[37]. Therefore, the preconditions in the tumor microenvironment to respond to immunotherapy are present in BM.

Patients with active BM from NSCLC have been excluded from pivotal clinical trials of immunotherapy in NSCLC, thus there is no high-level evidence available from the prospective studies. However, in the Keynote 24, the Keynote 189 (trials of pembrolizumab in the frontline), and the OAK trial (atezolizumab in the second-line setting), patients with previously treated brain metastasis were allowed to be enrolled. Specific intracranial response was not available, but the OS benefit seemed to have been equally sustained[26,32,38]. The expanded access program (EAP) of nivolumab in Italy included a cohort of 409 NSCLC patients with symptomatic or controlled BM. The real-world experience demonstrated ORR of 17% and DCR of 40% respectively, similar to the whole population of 1588 patients with median OS of 8.6 months and 11.3 months, respectively[39]. These results seem to suggest the overall benefit was able to be retained in the subgroup of patients with BM. However, it remains unknown from these trials to what extent the intracranial control derives directly from immunotherapy.

In a retrospective study, 43 NSCLC patients with BM were included, and 16 patients had active BM. Patients treated with nivolumab achieved an ICRR and an extracranial RR of 9% and 11%, respectively. The median intracranial and the general PFS were 3.9 months and 2.8 months, respectively[40]. Although the RR was rela-

tively low, these were real-world unselected cases without known PD-L1 status and the PFS was in line with pivotal immunotherapy trials in the 2nd-line setting. More importantly, the RR appears to be equivalent for both intracranial and extracranial disease.

The single-agent activity of pembrolizumab in the brain was also studied in a phase II trial including both NSCLC and melanoma patients with at least 1 BM between 5 and 20 mm that was asymptomatic and either untreated or progressing after prior local therapy. The result was recently updated at 2018 ASCO annual meeting[41,42]. Two cohorts of NSCLC patients were enrolled with 34 PD-L1 positive (PD-L1 ≥ 1%) patients in cohort 1, and 5 PD-L1 negative or unevaluable patients in cohort 2. Pembrolizumab 10 mg/kg was administered every 2 weeks. None of the patients had previously received immunotherapy. 10 of 34 (29.4%) patients in cohort 1 had a response in CNS. Interestingly, 7 patients had discordance between CNS and systemic responses (4 with PD in brain and PR in body, and 3 with PR in brain and PD in body). Intracranial PFS among patients with BM response or stable disease was 10.7 months. Median OS among all patients was 8.9 months, with 31% of patients living at least 2 years. No patients in cohort 2 had a BM response, but 2 of the 5 patients lived past 1 year. Treatment was well-tolerated, with no neurologic adverse events (AEs) > grade 1 related to treatment, although 2 patients developed grade 3 pneumonitis related to pembrolizumab[42]. Although large prospective studies are lacking, taken together, it appears that a PD1 inhibitor can have activity in brain and may be a safe and active treatment option for patients with small, asymptomatic BM in NSCLC patients.

The role of immunotherapy has been more extensively studied in melanoma patients with BM. Ipilimumab, a CTLA4 inhibitor, achieved intracranial disease control in 12/51 (24%) patients in patients with asymptomatic small BM without steroid use[43]. More recently, two phase 2 studies combining nivolumab and ipilimumab were investigated in the same patient population. The Checkmate 204 study comprised short-term follow-up of 75 asymptomatic patients. The ICRR was 56% with 20% of patients experiencing CR[44]. In an Austrialian study, 35 and 25 patients with asymptomatic BM and no previous immunotherapy were randomized to cohort A (nivolumab plus ipilimumab) and B (nivolumab only), respectively. 16 patients in whom local therapy had failed or who had neurological symptoms or leptomeningeal disease were enrolled in cohort C[45]. The ICRR, CR for cohort A was 46% and 17%, respectively. The median intracranial PFS was not reached at data cutoff. Of note, for treatment-naïve patients, the ICRR was 56%. By contrast, the cohort B of 25 patients receiving nivolumab only had ICRR of 20% and CR of 12%, respectively with median intracranial PFS of 2.5 months[45]. In contrast to cohort A and B, only one of 16 patients in cohort C had intracranial response (6%) and this patient had BRAF wild type, no leptomeningeal disease and neurological symptoms only[45]. As expected, more treatment-related adverse events (AEs) happened in cohort A patients who received combination. Three patients (9%) in cohort A and one patient in cohort C (6%) developed peripheral neuropathy. Grade 3 AEs occurred in 54% of cohort A, 16% of cohort B and 13% of cohort C and the most common AEs were diarrhea or colitis, and hepatitis. Three patients in cohort A experienced grade 4 hepatitis, pulmonary edema or hypophysitis. One patient in cohort B and one patient in cohort C experience severe headache due to cerebral edema. No death occurred because of study treatment[45]. No CNS demyelination occurred, although it was reported previously in a patient treated with nivolumab after progressing on ipilimumab[46]. These results suggest that combination immunotherapy with ipilimumab and nivolumab may represent a valuable option in patients with asymptomatic melanoma brain metastases, long-term follow-up with OS data is eagerly awaited[45].

FUTURE PERSPECTIVE

In general, the response of systemic (extra-cranial) disease correlates well with that of intracranial BM with immunotherapy although discordance has been reported[42,45]. Using the available biomarkers, we might be able to tease out the patients with asymptomatic small BM who might respond well to immunotherapy or an immunotherapy combination. At this time, there are no data demonstrating the use of combination immu-

notherapy in NSCLC with BM. However, as aforementioned, the Checkmate 227 study exhibited great activity of nivolumab-ipilimumab combination against NSCLC with high TMB[28]. Extrapolating from melanoma studies, it is conceivable that the same combination might be able to confer a much higher and more durable response in NSCLC with BM and high TMB. In the Keynote 189 trial using platinum/pemetrexed/pembrolizumab, the hazard ratio in the subgroup of 108 patients with BM was impressive 0.36, suggesting chemo-immunotherapy could represent an effective option for this group, although PDL1 status was unknown[26]. For the PD-L1 ≥ 50% subgroup, the RR was over 60%, with a disease control rate almost up to 90%[26]. This treatment combination might also provide a great ICRR and durable IC PFS given that both chemotherapy and immunotherapy have been shown to be effective against BM in NSCLC. Furthermore, how to incorporate and/or sequence SRS in the context of immunotherapy remains unanswered. Prospective studies are needed to address these burning questions, and future adoption of immunotherapy or immunotherapy combinations as the first-line therapy in the appropriate patient population with BM may change our current clinical practice and the use of WBRT or SRT.

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