Editorial

Management of brain metastases in non-small cell lung cancer without actionable driver mutations—the need to dive deeper in the right 'pool'

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Comment on: Chen M, Wei L, Wang Q, *et al.* Efficacy of different therapies for brain metastases of non-small cell lung cancer: a systematic review and meta-analysis. Transl Lung Cancer Res 2023;12:689-706.

Keywords: Brain metastases (BMs); non-small cell lung cancer (NSCLC); mutation naïve; mutation negative; brain radiotherapy (brain RT)

Submitted Sep 02, 2023. Accepted for publication Sep 14, 2023. Published online Oct 25, 2023.
doi: 10.21037/tlcr-23-571
View this article at: https://dx.doi.org/10.21037/tlcr-23-571

Non-small cell lung cancer (NSCLC) represents more than 80% of all lung cancer cases, remaining the leading cause of cancer-related mortality worldwide (1). According to the Surveillance, Epidemiology and End Results (SEER) database (2), 9.6% of patients with lung cancer are diagnosed with brain metastases (BMs) during the staging workup, and 13.5% develop BMs over the lifetime, with NSCLC representing the most common histology for synchronous BMs diagnosis (13.4%). BMs remain an important cause of morbidity and mortality, with rising incidence due to improved detection with advanced imaging techniques and surveillance programs. Moreover, recent advances in systemic therapies have led to prolonged overall survival (OS) and improved rates of extracranial disease control in lung cancer patients.

The cumulative incidence of BMs is higher in NSCLC patients with oncogenic driver alterations [epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement], with more exhaustive data on the efficacy of targeted therapy with tyrosine kinase inhibitors (TKIs) in these patients (3). In the absence of actionable driver mutations, the treatment of new or progressive BMs remains a gray area. This subgroup represents approximately 60% of all NSCLC cases (4). The use of immune checkpoint inhibitors (ICIs) has paved a new way for the treatment of metastatic NSCLC, with significant improvement in survival and quality of life (5,6). The current standard of care (SOC) for non-oncogenic driver mutated advanced metastatic NSCLC with programmed death-ligand 1 (PD-L1) tumor proportion score (TPS) ≥50% is ICI monotherapy with pembrolizumab (5) or atezolizumab (7,8), or pembrolizumab with pemetrexed and platinum-based chemotherapy in non-squamous NSCLC (6), and carboplatin-paclitaxel/nab-paclitaxel chemotherapy in squamous histology (9), cemiplimab (10), nivolumab plus ipilimumab (11), durvalumab +/– tremelimumab (12).

Current literature exploring the use of systemic agents [chemotherapy alone or chemotherapy plus immunotherapy (IO)] in combination with local brain therapies, i.e., radiotherapy (RT) with or without surgery for NSCLC-BMs, provides compelling data. The scarcity of prospective data along with factors like heterogeneity in NSCLC population and treatment regimens represent a challenge in data interpretation and drawing conclusions. Thus, the idea of conducting a systematic review and meta-analysis focusing on the available evidence in

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driver mutation-negative NSCLC population seems appropriate and justified. The current study "Efficacy of different therapies for brain metastases of non-small cell lung cancer: a systematic review and meta-analysis" by Chen and colleagues (13), aimed to review the available data on potential benefits of different systemic agents in combination with brain RT for BMs in this clinical setting.

Why is treating BMs particularly a challenge? Rationale behind using ICIs for BMs

Blood-brain barrier (BBB) has been presumed to be impermeable to anti-cancer agents with large molecular weight and low solubility, owed to its epithelial-like tight junctions within the capillary endothelium (14). ICIs help in potentiating the host's own immune response against tumor cells. Dense tumor infiltrating lymphocytes (TILs) infiltrates are common in BMs and correlate with peritumoral edema and prognosis (15). Since ICIs act by removing the inhibition of T cells by tumor cells, immune cell trafficking of peripherally activated T cells into the central nervous system (CNS) is perhaps more critical than the penetration of the blood-brain barrier by the ICIs themselves (16,17).

Management of BMs: why should we integrate local and systemic therapy

The term 'oligometastasis' (18), has helped identify a group of patients who may benefit from an aggressive local approach to their metastases in addition to systemic therapy, thus improving overall prognosis. Oligometastatic disease (OMD) has been defined as having up to five lesions occurring separately and distributed in up to three organs (19). Stereotactic ablative radiotherapy (SABR) has shown improvement in long-term outcomes in patients with OMD (20), however there is paucity of data regarding ablative treatment of asymptomatic BMs in this cohort. Stereotactic radiosurgery (SRS) has become the treatment of choice for 1–3 BMs with local control rates of 70–90% (21). There is supportive data for SRS use in patients with 4–15 BMs, providing a reduced risk of cognitive decline compared to whole brain radiotherapy (WBRT) without compromising OS (NCT015992968). There is some evidence for synergy between SRS and IO leading to improved intracranial control (22,23), though solid prospective data is still deficient.

Reliable evidence on the efficacy of ICIs in BMs in mutation-negative NSCLC

Most IO trials have excluded patients with active, untreated or symptomatic BMs (5,6,24-27). In the pivotal ICI trials, patients were not stratified based on the presence of BMs, and only a few trials had a preplanned BMs subgroup analysis. The intracranial efficacy of ICIs was not reported in these studies.

A non-randomized Phase II trial demonstrated CNS activity of pembrolizumab and BMs response rates of 29.7% in NSCLC patients with PD-L1 expression ≥1% (28). In another prospective study, a subgroup analysis of ipilimumab plus nivolumab showed significant efficacy against BMs in NSCLC patients with no actionable driver mutations (11).

Checkmate 227 (29) was a Phase III trial that evaluated ipilimumab plus nivolumab in advanced NSCLC with PDL1 expression of ≥1%, however only 10% of recruited patients harbored BMs. In the recently reported post hoc exploratory intracranial efficacy outcomes, ipilimumab plus nivolumab was found to be effective as first-line treatment in patients with treated BMs, at 5 years of follow up (30).

Hendriks *et al.*, prospectively collected data on 1,025 NSCLC patients who received ICIs, across 5 European centers. Overall response rates in patients with BMs were found to be similar to those without BMs (31). Most of the evidence comes from expanded access programs (EAPs) or from small retrospective series, as enumerated in the present meta-analysis by Chen and colleagues.

Practical challenge of using ICIs in symptomatic BMs

Patients with symptomatic BMs require medical decompression with steroids. The immunosuppressive effect of corticosteroids may reduce the efficacy of PD-(L)1 blockade. Large institutional reviews have demonstrated poorer outcomes (32) due to modulation of peripheral blood immune cells (33) in patients with advanced NSCLC treated with baseline corticosteroid use of ≥10 mg of prednisone equivalent.

Critical analysis of the present study

First, we commend the authors for conducting a comprehensive search in an overt gray area. It should

be recognized that patients with BMs from NSCLC constitute a heterogeneous cancer population, which makes it challenging to report uniform and representative data regarding the intracranial outcomes. Upon critical review of this meta-analysis, the following concerns are raised:

(I) Most of the published studies on BMs from NSCLC include patients with oncogenic driver mutations and only a few exclusively analyze the subgroup that is driver mutation naïve. Specifically, the proportion of the population with driver-gene mutation was required to be <25% in each study included in the meta-analysis, though the authors decided to include one study in which patients with EGFR or KRAS mutation represented 40.5% of the whole study population. The authors justify this decision by similarity in the intracerebral objective response rate (icORR) when compared to the prospective study by Goldberg *et al.* (28). Inevitably, this further widens the gap in baseline heterogeneity, demonstrating the evident challenge of solely analyzing the driver mutation-negative NSCLC population.

(II) The type of systemic agents and combination or addition of brain therapies varies widely between the selected studies. Also, information on the type of brain therapy delivered is widely lacking. This meta-analysis includes studies that administered chemotherapy alone and chemotherapy in combination with RT, which were conducted before the results of the Keynote 024 and Keynote 189 trials that established ICIs as the treatment of choice in stage IV NSCLC patients. Two studies reported institutional data with chemotherapy and ICIs but did not include any information on the administration and type of local treatment to the BMs. Most of them did not account for the key difference in delivering WBRT or SRS, plus the systemic therapy. Two studies evaluated patients who received SRS with ICIs (34); one of which compared WBRT and SRS in 30 patients from 15 studies (35). SRS is offered to patients with limited intracranial spread, favorable prognosis, and good functional status at baseline, whereas WBRT is usually reserved for patients with radiological evidence of widespread disease in the brain. Therefore, icORR is a metric that is inevitably influenced by the modality of brain RT delivered. Hence, pooling data on brain outcomes under one RT group is the biggest downside of the present meta-analysis, given the bias introduced. The primary endpoints following a specific type of RT (focal RT, i.e., SRS or hypofractionated stereotactic RT versus WBRT, with or without the hippocampal avoidance as a memory-sparing strategy) as part of BMs treatment should be accompanied by the assessment of the quality of life, which was largely omitted in all the included studies.

(III) It is essential to mention that the initial status of intracranial disease (the number and size of BMs), as well as the response following the initial brain RT, are well-established predictors of the recurrence risk and overall prognosis in patients with BMs. This means that at the study baseline, one must assume that patients have unequal chances of achieving intracranial control or, in other words, the duration of BMs response may vary. This is difficult to control for, though strategies such as conducting a subgroup analysis or stratification according to the total volume of intracranial disease at diagnosis or calculating the BM velocity should be strongly taken into consideration.

(IV) A meta-analysis should combine and synthesize multiple studies, with the aim to integrate their results. Conducting such study with the best available evidence, where many aspects are yet to be improved, may not be enough to provide solid answers to the research question raised and not a sufficient solution to "fix" the uncertainties and inhomogeneity present in the published literature of relevance. Since any group of studies may be a subject to a systematic review and any data can be combined in a meta-analysis, it is important to critically assess the potential aspects that negatively affect the validity and reproducibility, and thus the final quality of this study. This is owed to the retrospective nature and small sample size of the studies analyzed. Confounding biases-are inherent to such reviews, which leads to imbalance in the factors associated with outcomes that must be acknowledged. The extensive heterogeneity comes across repeatedly in all subgroup analysis.

Assessing the efficacy of ICIs towards influencing intracranial outcomes in locally treated mutation-naive NSCLC-BMs, may not be feasible in the absence of a

carefully designed clinical trial. While designing such trials involves stringent selection criteria and homogenous BMs study population, it may be far from reflecting the real-life clinical practice and may, on the other hand, not be generalizable. Only single-arm prospective, observational, or real-world data studies may provide an insight into real life clinical practice.

To conclude, the meta-analysis by Chen *et al.* integrates and summarizes the evidence available to identify an area in which more research is still needed. It selects the pertinent studies by carrying out a systematic review, though the accuracy and the quality of the individual studies remain low. Finally, it provides an estimated effect, drawing general conclusions. Overall, the main findings confirm that the combination of ICIs and RT has the most significant synergistic effect and the highest intracranial response rates. They prove that this effect is most significant in patients with PDL1 ≥50% or first-line treatment groups. This is consistent with previously reported data and has been highlighted in a higher quality design study as is the present meta-analysis, in the light of the available evidence. The high number of biases, mainly due to heterogeneity, should be addressed, if possible, in future studies.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Lung Cancer Research*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-571/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Jablonska PA, Das A. Management of brain metastases in non-small cell lung cancer without actionable driver mutations—the need to dive deeper in the right 'pool'. Transl Lung Cancer Res 2023;12(10):1966-1971. doi: 10.21037/tlcr-23-571