Editorial on Immunotherapy and Tumor Microenvironment

Brain metastases: lessons and challenges in the targeted therapy and immunotherapy era

Peter Kar Han Lau

Medical Oncology Department, Peter MacCallum Cancer Centre, Melbourne, Australia

Correspondence to: Dr. Peter Kar Han Lau. Consultant Medical Oncologist–Melanoma and Skin Unit, Post Graduate Scholar, Medical Oncology Department, Peter MacCallum Cancer Centre, Victorian Comprehensive Cancer Centre, 305 Grattan Street, Melbourne, Victoria 3000, Australia. Email: Peter.Lau@petermac.org.

Submitted Mar 04, 2020. Accepted for publication May 08, 2020.
doi: 10.21037/jtd-2019-itm-012
View this article at: http://dx.doi.org/10.21037/jtd-2019-itm-012

Developments during the previous decade in melanoma and lung cancer headlined an explosion of new molecular targeted therapies and the arrival of immunotherapy as a mainstay of cancer treatment. Melanoma saw unprecedented improvements in survival outcomes with rapid development of combination BRAF-MEK inhibitors alongside immune-checkpoint inhibitors targeting the CTLA-4 and anti-programmed-death-1 axis (PD1) (1,2). Lung cancer followed suit with the development of anti-PD1/anti-PDL1 as monotherapy (3-5), in combination with chemotherapy (6,7) and with anti-CTLA-4 (8). Furthermore, a plethora of molecular targeted therapies against ALK such as crizotinib, alectinib, ceritinib, brigatinib and lorlatinib together with the development of the third generation EGFR inhibitor osimertinib are now firmly established in the lung cancer armamentarium. However, melanoma and lung cancer exhibit the highest rate of brain metastases of all solid malignancies and remains a challenging clinical problem. While patients with brain metastases have ordinarily been excluded from Phase III registration trials, the Food and Drug Administration recently released a draft document recommending inclusion of such patients (9). Hence the new decade brings upon a new challenge of improving outcomes of patients with brain metastases.

The brain exhibits a unique tumour micro-environment for two major reasons: the presence of the blood brain barrier that protects the CNS from most drugs or toxins and secondly the brain's unique cellular composition (10). The blood brain barrier comprises of endothelial cells that are connected by continuous tight junctions. The end feet of astrocytes ensheath the endocytes and together with pericytes located at the basement membrane form a protective barrier that blocks most small molecules. Compared to extracranial sites, the brain parenchyma comprises of vastly different inflammatory cells dominated by macrophages. Chief amongst these macrophages are microglia that are brain specialised macrophages that persist throughout life with spindle like extensions that are able to surveil the parenchyma. Furthermore, astrocytes and other glial cells are unique to the brain and as such the tumour microenvironment is unique compared to other anatomical sites. These considerations shape small molecule drug delivery to the brain and also have potential implications on immunotherapy.

Local therapy such as radiation and surgery have traditionally been the mainstays of brain metastasis management but systemic therapies have now entered the treatment paradigm particularly with ALK rearranged NSCLC. Second generation ALK tyrosine kinase inhibitors such as alectinib and brigatinib were specifically designed to penetrate the blood-brain barrier; a key shortcoming of the first generation crizotinib. These newer agents display clear superiority over crizotinib with impressive intracranial response rates and prolonged progression free survival. In patients with measurable brain metastases in the ALEX study, alectinib exhibited an intracranial response rate of 81% (17/21) versus 50% (11/22) with crizotinib. Duration of CNS response to alectinib was also prolonged at approximately 17.3 months compared to 5.5 for crizotinib (11). Moreover 40% (n=122) of the entire study population possessed any brain metastases at baseline, but landmark 12-month CNS progression was strongly in favour

of alectinib at 9.4% versus 41.4% for crizotinib. Similarly of 39 patients with measurable brain metastases in the ALTA-1L study, brigatinib exhibited an intracranial response rate of 78% versus 26% with crizotinib (12). Median intracranial progression free survival was not reached with brigatinib and the second generation inhibitor was associated with a lower rate of CNS progression compared to crizotinib (9% versus 19% respectively). Unpublished data suggests ceritinib also possesses encouraging intracranial activity in ALK rearranged NSCLC from the ASCEND-7 trial with an intracranial response rate of 52% with median duration of 7.5 months (13). High intracranial activity is not only restricted to ALK rearranged, but also EGFR mutant NSCLC. Patients with measurable intracranial metastases in the FLAURA study had a response rate of 91% (20/22) to osimertinib (14). As such systemic therapy for brain metastases in ALK and EGFR mutant NSCLC can be considered as first line therapy—foregoing the need for local therapy unless the patient is grossly symptomatic with high volume disease.

Given the majority of NSCLC does not possess a readily targetable oncogene such as EGFR or ALK, can immunotherapy therefore play a role in patients management of CNS metastases without an ALK or EGFR oncogenes? The only formal study addressing this question is a single arm Phase II study of 18 patients with asymptomatic NSCLC brain metastases which demonstrated an intracranial response rate of 33% with median duration of response of 10.7 months (15). On the surface this appears a promising result, however the trial was a single institution study and patient PD-L1 status was not assessed using an approved FDA assay. The melanoma experience with anti-PD1 monotherapy in brain metastases also provides caution: single agent nivolumab and pembrolizumab elicited an intracranial response rates of 20% (5/25) and 26% (6/23) respectively which is half the anticipated extracranial response rate of approximately 40% (16,17). Hence the utility of anti-PD1 monotherapy for NSCLC brain metastases without additional local therapy is questionable. Given responses to immune checkpoint inhibitors can take 2–3 months, combination chemotherapy with anti-PD1/PDL1 and local therapy should be employed in NSCLC brain metastases without an EGFR or ALK rearrangement.

Despite the explosion of immunotherapy combinations in NSCLC, there are few translational studies that explore the tumour microenvironment of brain metastases. Recently Kudo *et al.*, performed Nanostring and complementary immunohistochemistry studies on 78 paired tumour samples of primary lung and intracranial metastasis from 39 patients (18). Most tumours were adenocarcinomas and a small proportion of samples were derived from never smokers. Differential gene expression suggested dendritic cell maturation, Th1 responses and leucocyte extravasation were downregulated in CNS metastases implying an immunosuppressive tumour microenvironment. Strikingly the CNS tumours exhibited a high proportion of macrophages ($CD68^+$) with lower CD8 T cells compared to the primary tumour. Whilst microglia are a major cellular player of the central nervous system micro-environment, additional immunohistochemistry with TMEM119; a specific microglia marker were invariably negative thereby confirming bone marrow derived macrophages as the predominant cell type. The abundance of both macrophages and microglia is also notable in glioblastoma multiformae (GBM) where they comprise between 25–80% of all cells in the tumour microenvironment depending on molecular subtype (19). Using semi-quantitative immunohistochemistry of 98 patients with GBM, $CD3^+$ T cells accounted for less than 5% of cells with low $CD8^+$ tumour infiltration that varied between 0.18% to 0.38% of the tumour area. B cells were rare, with only 4 patients exhibiting any evidence of this cell type. The importance of macrophages is unclear, with early studies suggesting this cell type might exhibit an immunosuppressive M2 phenotype (20), although this finding was not replicated in a study of freshly acquired tumours (21). With an abundance of macrophages, inhibition of colony-stimulating factor-1 receptor (CSF-1R) could potentially be advantageous. Further studies are required to delineate the brain metastasis tumour microenvironment and whether these observations in GBM are similar to NSCLC and its molecular subtypes.

Recent investigations in melanoma brain metastases, might provide additional insights into NSCLC. Fischer *et al.* demonstrated a mismatch in immune cell populations between melanoma brain metastases and other extracranial sites (22). Even when lymph node deposits were excluded, melanoma brain metastases exhibited fewer CD3, $CD8^+$, dendritic cells and macrophages compared to extracranial metastases. Interestingly analysis of well described candidates of immunosuppression in melanoma such as loss of PTEN and beta catenin signalling did not correlate with a relatively "cooler" CNS tumour microenvironment. Rather an upregulation of oxidative phosphorylation pathways was found to correlate with the immunosuppressive

melanoma brain microenvironment. Subsequent mouse models of brain metastases treated with an oxidative phosphorylation inhibitor showed improved survival; surprisingly the CNS tumour was controlled, but primary tumour and lung metastases growth was unchanged (22). An interesting hypothesis is whether oxidative phosphorylation pathway upregulation in melanoma CNS metastases induces "metabolic starvation" of surrounding immune cells in the tumour microenvironment.

As mentioned above, anti-PD1 monotherapy intracranial responses are substantially less than extracranial sites in melanoma. However, combination ipilimumab-nivolumab possesses near equivalent intracranial and extracranial response rates at approximately 55% albeit in populations with asymptomatic and relatively low volume brain metastases (16,23). Insufficient T cell priming of CNS metastases might account for the discrepant response rates with anti-PD1. Whether this is due to impaired antigen presenting cell function or other suppressive factors is unclear. In a murine melanoma model, intracranial responses to combination anti-CTLA-4 and anti-PD1 occurred only in the presence of an extracranial metastasis (24). Furthermore, responses by combination immunotherapy against murine GBM and melanoma brain metastases were boosted by the addition of a vascular endothelial growth factor-c construct that enhanced development of cranial lymphatic vessels draining to deep cervical lymph nodes (25). Collectively these two studies suggest the unique anatomical structure of the brain limits T cell priming required for immunotherapy responses. Anti-CTLA-4 might enhance T cell priming within the CNS draining lymph nodes and when given in combination with anti-PD1, increases CD8 cytotoxic T cells, into the tumour (24). Depletion of CD8 and natural killer cells did negate responses to combination anti-CTLA-4 with anti-PD1 indicating the requirement of cytotoxic cells for intracranial responses reminiscent of extracranial metastasis studies. Clinical correlation of these findings is naturally limited by the practicalities of intracranial biopsy but murine models can provide some insight into this difficult to study area.

With the great advances in small molecule inhibitors and immunotherapy, the long held dogma of the brain representing a "sanctuary" site for advanced cancer is being broken down. However, much work remains to be done with respect to investigations of the mechanisms of CNS metastasis. Furthermore, the role of microglia, macrophages and the entire interplay of CNS tumour microenvironment remains under investigated. With the growing recognition of the brain representing a unique tumour microenvironment, and increasing inclusion of patients with CNS metastases in clinical trials sets the stage for a new decade of dynamic cancer research.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Guest Editors (Clare Y. Slaney, Jian Zhang and Peng Luo) for the series "Immunotherapy and Tumor Microenvironment" published in *Journal of Thoracic Disease*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-2019-itm-012). The series "Immunotherapy and Tumor Microenvironment" was commissioned by the editorial office without any funding or sponsorship. PKHL reports personal fees from Bristol Myers Squibb and Pfizer outside the submitted work. The authors have no other conflicts of interest to declare.

Ethical Statement: The author is 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.

References

1. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015;373:23-34.
2. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone

in melanoma. N Engl J Med 2014;371:1877-88.
3. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255-65.
4. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33.
5. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer. N Engl J Med 2015;373:123-35.
6. Reck M, Mok TSK, Nishio M, et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. Lancet Respir Med 2019;7:387-401.
7. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med 2018;378:2288-301.
8. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2019;381:2020-31.
9. FDA. Cancer Clinical Trial Eligibility Criteria: Brain Metastases. In: Guidance Document. Food and Drug Administration. 2019. Accessed 1/12/2019. Available online: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cancer-clinical-trial-eligibility-criteria-brain-metastases
10. Sampson JH, Gunn MD, Fecci PE, et al. Brain immunology and immunotherapy in brain tumours. Nat Rev Cancer 2020;20:12-25.
11. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non–Small-Cell Lung Cancer. N Engl J Med 2017;377:829-38.
12. Camidge R, Kim HR, Ahn MJ, et al. Brigatinib vs crizotinib in patients with ALK inhibitor-naive advanced ALK+ NSCLC: Updated results from the phase III ALTA-1L trial. Ann Oncol 2019;30:ix195-6.
13. Chow LQ, Barlesi F, Bertino EM, et al. Results of the ASCEND-7 phase II study evaluating ALK inhibitor (ALKi) ceritinib in patients (pts) with ALK+ non-small cell lung cancer (NSCLC) metastatic to the brain. Ann Oncol 2019;30:v602-3.
14. Reungwetwattana T, Nakagawa K, Cho BC, et al. CNS Response to Osimertinib Versus Standard Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. J Clin Oncol 2018. doi: 10.1200/JCO.2018.78.3118.
15. Goldberg SB, Gettinger SN, Mahajan A, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. Lancet Oncol 2016;17:976-83.
16. Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol 2018;19:672-81.
17. Kluger HM, Chiang V, Mahajan A, et al. Long-Term Survival of Patients With Melanoma With Active Brain Metastases Treated With Pembrolizumab on a Phase II Trial. J Clin Oncol 2019;37:52-60.
18. Kudo Y, Haymaker C, Zhang J, et al. Suppressed immune microenvironment and repertoire in brain metastases from patients with resected non-small-cell lung cancer. Ann Oncol 2019;30:1521-30.
19. Martinez-Lage M, Lynch TM, Bi Y, et al. Immune landscapes associated with different glioblastoma molecular subtypes. Acta Neuropathol Commun 2019;7:203.
20. Komohara Y, Ohnishi K, Kuratsu J, et al. Possible involvement of the M2 anti-inflammatory macrophage phenotype in growth of human gliomas. J Pathol 2008;216:15-24.
21. Gabrusiewicz K, Rodriguez B, Wei J, et al. Glioblastoma-infiltrated innate immune cells resemble M0 macrophage phenotype. JCI Insight 2016;1:e85841.
22. Fischer GM, Jalali A, Kircher DA, et al. Molecular Profiling Reveals Unique Immune and Metabolic Features of Melanoma Brain Metastases. Cancer Discov 2019;9:628-45.
23. Tawbi HA, Forsyth PA, Algazi A, et al. Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain. N Engl J Med 2018;379:722-30.
24. Taggart D, Andreou T, Scott KJ, et al. Anti-PD-1/anti-CTLA-4 efficacy in melanoma brain metastases depends on extracranial disease and augmentation of CD8(+) T cell trafficking. Proc Natl Acad Sci U S A 2018;115:E1540-9.
25. Song E, Mao T, Dong H, et al. VEGF-C-driven lymphatic drainage enables immunosurveillance of brain tumours. Nature 2020;577:689-94.

Cite this article as: Lau PKH. Brain metastases: lessons and challenges in the targeted therapy and immunotherapy era. J Thorac Dis 2020;12(8):4527-4530. doi: 10.21037/jtd-2019-itm-012

