Brain metastases (BMs) are the most common intracranial neoplasms. The estimated incidence of BMs in lung cancer is 15–30% and is increasing as outcomes improve with the advent of molecularly targeted therapies (1). BMs are more frequent in non-small cell lung cancers (NSCLCs) with oncogenic driver mutations like epidermal growth factor receptor (EGFR)-mutation or anaplastic lymphoma kinase (ALK)-rearrangement, ranging between 25% at diagnosis to more than 45% three years post diagnosis (2). Historically, survival in NSCLC with BMs has been poor (3) but has improved with recent advancements. Both EGFR-mutation and ALK-rearrangement are prognostic factors incorporated in prognostic assessment and associated with better survival in NSCLC with BMs (4).

Surgery and radiation therapy (RT) are the standards of care treatment options for BMs, but the paradigm is changing in NSCLC with genomic alterations and associated targeted therapies. Up to 69% of advance NSCLC could have a potentially actionable molecular target (5). In this review, we will discuss the current treatment options for BMs from NSCLC with driver mutations, focusing on EGFR-mutation.
RT

RT has historically been considered the cornerstone for treatment of multiple BMs secondary to NSCLC. Whole brain radiation therapy (WBRT) has been the traditional approach but stereotactic radiosurgery (SRS), which delivers high doses of radiation to the target volume while avoiding surrounding tissue, has become the preferred approach. Median survival in NSCLC patients treated with WBRT ranges between 4 to 6 months (6,7). SRS was initially evaluated for safety as a salvage therapy in patient previously treated with WBRT and subsequently showed survival benefit in patient with single BM in combination with WBRT (8). Further studies comparing SRS alone to SRS plus WBRT demonstrated similar overall survival (OS) of 8 to 10 months, higher rates of intracranial failure with SRS alone, and worse cognitive outcomes with WBRT (9,10). Another study among patients with fewer than 4 BMs less than 4 cm in size (n=189 for NSCLC) comparing SRS with WBRT showed a longer survival among those treated with SRS (11). Therefore, SRS is preferred treatment modality for limited BMs. There is some evidence to support use of SRS in multiple (>3) BMs. A prospective non-inferiority study evaluated SRS in 1,194 patients comparing 2–4 and 5–10 BMs (<3 cm in longest diameter; total cumulative volume ≤15 mL). Results showed that the OS (10.8 months) and treatment-related adverse events did not differ between the two groups of patients (12).

EGFR-mutated NSCLC

EGFR-mutations occur in 10–20% of non-Asians and in about 40% of Asian patients (5). Multiple randomized controlled trials (RCTs) have established the superiority of EGFR TKI as the first line systemic treatment in advance stage EGFR-mutated NSCLC compared to chemotherapy (13-16). Different generations of EGFR TKIs are available: First-generation (Gefitinib, Erlotinib), second-generation (Afatinib) and third-generation (Osimertinib).

Multiple studies have shown better activity in the central nervous system (CNS) with first and second-generation EGFR TKI compared to cytotoxic chemotherapy (17,18). A retrospective study of 306 NSCLC patients compared efficacy of three EGFR TKI. The cumulative incidences of subsequent BM at 6, 12, and 24 were 3.8%, 13.9%, and 34.6%, respectively, in the gefitinib group; 5.6%, 9.3%, and 9.3%, respectively, in the erlotinib group; and 0%, 2.8%, and 28.3%, respectively, in the afatinib group, indicating no significant difference (P=0.80) (19).

In the randomized FLAURA trial, Osimertinib when compared with first-generation EGFR TKI demonstrated better BBB penetration, higher rate of intracranial response (66% vs. 43%) and a lower rate of CNS progression (20,21). The median PFS (18.9 vs. 10.2 months) and median duration of response (17.2 vs. 8.5 months) was significantly longer with osimertinib than with first-generation EGFR TKI. Therefore, Osimertinib is the recommended first line systemic treatment for advanced EGFR-mutated NSCLC.

In this current era of targeted therapies like tyrosine kinase inhibitors (TKIs), advanced EGFR-mutated NSCLC have improved median survival of 30 months (22). This is associated with high intracranial response to EGFR TKI and concern of neurologic side effects with radiation, is shifting the treatment paradigms in EGFR-mutated NSCLC with BM. While historically, RT was standard first line treatment for BMs, currently data is limited and controversial to recommend either use of upfront RT or EGFR TKI.

A 2015 meta-analysis of 12 observational studies exclusively including 363 patients with EGFR-mutant NSCLC with BMs found that, compared with upfront treatment with first-generation EGFR TKI, upfront cranial radiation results in similar overall intracranial response rate, improved 4-month intracranial PFS, improved 2-year OS but caused more neurological adverse events (23). A retrospective multi-institutional analysis of 351 TKI-naive EGFR-mutated NSCLC with BM compared three treatment groups: SRS followed by EGFR TKI, WBRT followed by EGFR TKI, or EGFR TKI followed by SRS or WBRT at intracranial progression. The median OS was improved for those receiving upfront SRS (n=100) at 46 months compared to upfront WBRT (n=120) at 30 months, or upfront EGFR TKI (n=131) at 25 months (P<0.001) (24). Another retrospective study on 104 advanced EGFR-mutated NSCLC patients with BM compared use of concurrent first-generation EGFR-TKI with WBRT with EGFR-TKI alone. While the median intracranial PFS significantly improved (17.7 vs. 11.0 months) there was no significant difference in median OS (28.1 vs. 24.0 months, P=0.756). Further subgroup analysis by the number of BMs found that median intracranial PFS was not significantly different between the two groups in patients with three or fewer BM (P=0.526) but improved in patients with >3 BM (P=0.001) (25). One retrospective study of 132 EGFR-mutated NSCLC patients with asymptomatic BM showed improved median OS (24.9 vs. 17.4 months, P=0.035) with
upfront radiation compared to upfront first-generation EGFR TKI (26).

These studies are representative of the data available, which is mostly retrospective and on first-generation EGFR TKI. Based on these studies, upfront SRS has better outcomes than upfront first-generation EGFR TKI. It is difficult to extrapolate this data to third-generation osimertinib given it has demonstrated higher intracranial activity compared to first-generation EGFR TKI but studies comparing osimertinib with radiation for the management of BM are lacking. Data on the use of EGFR TKI in symptomatic BMs or combining them with SRS is also limited as patient included in the trials had already treated or asymptomatic BMs. Clinical trials are ongoing to compare osimertinib with and without radiation in NSCLC patients with BM (NCT03769103 and NCT03497767).

Conclusions

With the advent of EGFR TKI, patients with advanced EGFR-mutated NSCLC are living longer with a median OS of 30 months. They also have a higher frequency of developing BMs. Data regarding combining and sequencing RT with EGFR TKI is limited and mostly on first-generation EGFR TKI, therefore should be interpreted carefully. Third-generation EGFR TKI like osimertinib is a reasonable first choice in newly diagnosed advanced EGFR-mutated NSCLC with BM given its CNS response rate, median PFS and duration of response. The use of SRS in an upfront setting can be considered in selected patients with symptomatic BMs. WBRT should be reserved as a last option due to potential neurocognitive side effects.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Lucyna Kepka) for the series “Radiotherapy for Brain Metastases from Lung Cancer” published in Journal of Thoracic Disease. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at: http://dx.doi.org/10.21037/jtd-2019-rbmlc-04). The series “Radiotherapy for Brain Metastases from Lung Cancer” was commissioned by the editorial office without any funding or sponsorship. GK reports personal fees from BMS, personal fees from Genentech, personal fees from Merck, personal fees from Astra Zeneca, personal fees from Eli Lilly, outside the submitted work. The authors have no other 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.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Cagney DN, Martin AM, Catalano PJ, et al. Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. Neuro Oncol 2017;19:1511-21.
2. Rangachari D, Yamaguchi N, VanderLaan PA, et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. Lung Cancer 2015;88:108-11.
3. Ali A, Goffin JR, Arnold A, Ellis PM. Survival of patients with non-small-cell lung cancer after a diagnosis of brain metastases. Curr Oncol 2013;20:e300-e306.
4. Sperduto PW, Yang TJ, Beal K, et al. Estimating Survival in Patients With Lung Cancer and Brain Metastases: An Update of the Graded Prognostic Assessment for Lung Cancer Using Molecular Markers (Lung-molGPA) Survival and Prognostic Ability in Lung Cancer With Brain Metastases Survival and Prognostic Ability in Lung Cancer With Brain Metastases. JAMA Oncol 2017;3:827-31.
5. Hirsch FR, Scagliotti GV, Mulshine JL, et al. Lung cancer: current therapies and new targeted treatments. Lancet 2017;389:299-311.
6. Suh JH, Stea B, Nabid A, et al. Phase III study of efaproxiral as an adjunct to whole-brain radiation therapy for brain metastases. J Clin Oncol 2006;24:106-14.

7. Mehta MP, Rodrigus P, Terhaard CH, et al. Survival and neurologic outcomes in a randomized trial of motexafin gadolinium and whole-brain radiation therapy in brain metastases. J Clin Oncol 2003;21:2529-36.

8. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet 2004;363:1665-72.

9. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol 2011;29:134-41.

10. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 2006;295:2483-91.

11. Halasz LM, Uno H, Hughes M, et al. Comparative effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for patients with brain metastases from breast or non-small cell lung cancer. Cancer 2016;122:2091-100.

12. Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol 2014;15:387-95.

13. Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J Clin Oncol 2011;29:2866-74.

14. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus cetuximab in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-34.

15. Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol 2014;15:213-22.

16. Zhou C, Wu YL, Chen G, et al. Final overall survival results from a randomised, phase III study of erlotinib versus chemotherapy as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802). Ann Oncol 2015;26:1877-83.

17. Heon S, Yeap BY, Lindeman NI, et al. The impact of initial gefitinib or erlotinib versus chemotherapy on central nervous system progression in advanced non-small cell lung cancer with EGFR mutations. Clin Cancer Res 2012;18:4406-14.

18. Schuler M, Wu YL, Hirsh V, et al. First-Line Afatinib versus Chemotherapy in Patients with Non-Small Cell Lung Cancer and Common Epidermal Growth Factor Receptor Gene Mutations and Brain Metastases. J Thorac Oncol 2011;6:380-90.

19. Su PL, Wu YL, Chang WY, et al. Preventing and treating brain metastases with three first-line EGFR-tyrosine kinase inhibitors in patients with EGFR mutation-positive advanced non-small cell lung cancer. Ther Adv Med Oncol 2018;10:397589.

20. 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. [Epub ahead of print].

21. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:113-25.

22. Okamoto I, Morita S, Tashiro N, et al. Real world treatment and outcomes in EGFR mutation-positive non-small cell lung cancer: Long-term follow-up of a large patient cohort. Lung Cancer 2018;117:14-9.

23. Soon YY, Leong CN, Koh WY, et al. EGFR tyrosine kinase inhibitors versus cranial radiation therapy for EGFR mutant non-small cell lung cancer with brain metastases: A systematic review and meta-analysis. Radiother Oncol 2015;114:167-72.

24. Magnuson WJ, Lester-Coll NH, Wu AJ, et al. Management of Brain Metastases in Tyrosine Kinase Inhibitor-Naive Epidermal Growth Factor Receptor-Mutant Non-Small-Cell Lung Cancer: A Retrospective Multi-Institutional Analysis. J Clin Oncol 2017;35:1070-7.

25. He ZY, Li MF, Lin JH, et al. Comparing the efficacy of concurrent EGFR-TKI and whole-brain radiotherapy vs EGFR-TKI alone as a first-line therapy for advanced EGFR-mutated non-small-cell lung cancer with brain
metastases: a retrospective cohort study. Cancer Manag Res 2019;11:2129-38.

26. Wang W, Song Z, Zhang Y. Efficacy of brain radiotherapy plus EGFR-TKI for EGFR-mutated non-small cell lung cancer patients who develop brain metastasis. Arch Med Sci 2018;14:1298-307.

Cite this article as: Bhandari S, Dunlap N, Kloecker G. Radiotherapy in brain metastases from EGFR-mutated non-small cell lung cancer. J Thorac Dis 2021;13(5):3230-3234. doi: 10.21037/jtd-2019-rbmlc-04