Review Article on Radiotherapy for Brain Metastases from Lung Cancer

Radiotherapy in brain metastases from EGFR-mutated non-small cell lung cancer

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Epidermal growth factor receptor (EGFR) mutations are present in 20–40% of non-small cell lung cancers (NSCLCs). Brain metastasis (BM) is more common in EGFR-mutated NSCLC (25–45%) compared to EGFR wild-type (15–30%). First and second-generation tyrosine kinase inhibitors (TKIs), such as erlotinib and afatinib have proven to be superior to chemotherapy in the front-line treatment of EGFR-mutated NSCLC. Osimertinib, a third-generation EGFR TKI, has demonstrated better blood brain barrier (BBB) penetration, higher rate of intracranial response (66% *vs.* 43%) and a lower rate of CNS progression when compared to first generation EGFR TKI. Evidence on upfront radiation *vs.* upfront osimertinib is limited, but rapidly evolving and being tested in ongoing comparative trials. Stereotactic radiation (SRS) is very effective in the control of BMs and has been increasingly used and consequently replacing resection of BMs. SRS also has been increasingly used in the treatment of multiple BMs. Considering the effectiveness of targeted agents such as third generation EGFR inhibitors clinicians now are more frequently faced with the decision, if systemic therapy is safe and effective enough to withhold SRS. Third generation EGFR inhibitors also have fewer adverse events as previous generations. This review discusses the current literature available for management of BM in EGFR-mutated NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); brain metastasis (BM); EGFR-mutated; radiation

Submitted Feb 20, 2020. Accepted for publication Oct 27, 2020.
doi: 10.21037/jtd-2019-rbmlc-04
View this article at: http://dx.doi.org/10.21037/jtd-2019-rbmlc-04

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 being 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 in 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-naïve 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.

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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