Editorial

The rapidly evolving treatment landscape for patients with brain metastases from epidermal growth factor receptor mutated non-small cell lung cancer

Anthony M. Brade[1,2]

[1]Department of Radiation Oncology, University of Toronto, Toronto, Canada; [2]Peel Regional Cancer Centre, Mississauga, Canada

Correspondence to: Anthony M. Brade. Division of Radiation Oncology, Peel Regional Cancer Centre, Mississauga, ON, Canada.
Email: anthony.brade@thp.ca.

Provenance: This is an invited Editorial commissioned by Guest Section Editor Dr. Shaohua Cui, MD (Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China).

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

Submitted Oct 10, 2017. Accepted for publication Oct 16, 2017.
doi: 10.21037/tlcr.2017.10.14
View this article at: http://dx.doi.org/10.21037/tlcr.2017.10.14

"May you live in interesting times"

While this quote is likely apocryphal and not, as is commonly attributed, a curse of Chinese origin (1), its ironic sentiment seems apt when one considers the rapidly shifting treatment landscape for patients with brain metastases. This is particularly true for non-small cell lung cancer, where systemic therapy is now frequently dictated by driver mutation-driven sub-categorization. The "seismic" changes in management for these groups of patients are being driven by the collision of two "tectonic" clinical forces: (I) development of molecularly-targeted, systemic therapies with clinically significant CNS activity; and (II) the shift towards tumour-targeted *vs.* whole brain radiotherapy (WBRT) [debated in (2,3)]. The resulting upheaval and emergence of a new "treatment geography" in this clinical space has made for "interesting times" indeed.

A recent paper by Magnuson *et al.* is case in point (4). It provides data addressing a key clinical conundrum: what is the optimal management for treatment-naïve patients with non-small cell lung cancer (NSCLC) adenocarcinoma presenting with brain metastases in the context of an epidermal growth factor receptor (EGFR)-mutated primary tumour? The authors retrospectively extracted data for 351 such patients treated at 6 clinical centres and evaluated their outcomes based on whether they were initially treated with an EGFR tyrosine kinase inhibitor (EGFR-TKI)—almost exclusively erlotinib in this study; WBRT; or stereotactic radiosurgery (SRS). All patients included in the analysis who received either WBRT or SRS started on EGFR-TKI after their radiotherapy, and all patients initially treated with EGFR-TKI therapy had to have received some form of RT as salvage treatment upon development of intracranial progression.

In an effort to address the well-known shortcomings of retrospective chart reviews, the authors carried out both multivariable and propensity-matched analyses, both of which produced congruent results. Not surprisingly, significant associations between survival and well known prognostic factors were found. These included significance for performance status, absence of extra-cranial disease, and age as well as the presence of exon 19 mutation (*vs.* 21). More notably, the analysis also documented dramatically improved survival in patients who received SRS as their initial treatment modality, despite controlling for these and other relevant factors, as well as a more modest improvement for patients treated with WBRT *vs.* EGFR-TKI. Patients treated upfront with EGFR-TKI had a median overall survival of 25 months; those treated with WBRT upfront—30 months; and those treated initially with SRS—46 months. The hazard ratio for patients receiving SRS initially *vs.* EGFR-TKI was 0.39 (95% CI, 0.26–0.58). This improvement in outcome was observed despite the fact that patients being treated with upfront SRS had larger brain metastases and were far more likely to be symptomatic from them (only 12% of patients

receiving upfront EGFR-TKI were symptomatic *vs.* ~50% for those receiving either SRS or WBRT).

Despite being well controlled and based on a large and relatively "clean" patient population, the study is obviously not definitive, the authors correctly point out that a confirmatory randomized study in this patient population is urgently needed. It does however, represent an important addition to the growing body of literature informing treatment decision making in this challenging group of patients. In recent years the field has largely shifted away from offering WBRT upfront due to concerns over treatment-related toxicity and its impact on quality of life. Undisputedly, the addition of WBRT to SRS or surgical resection for limited numbers of metastases (1-3) reduces the rate of intracranial disease progression, both local and distant (5-8). However, as these recent randomized studies demonstrate, at least in the population of patients with limited metastases, SRS alone as an upfront option offers improved neurocognitive function compared to the combination of SRS and WBRT with at least equivalent overall survival. Relevant to this editorial, it should be pointed out that while the randomized studies referenced include most solid tumour histologies, NSCLC patients make up the largest single group amongst those accrued.

The patients included in the Magnuson paper represent a highly selected, in fact the best, prognostic subgroup of NSCLC patients with brain metastases which raises questions regarding directly comparability to those included in the randomized studies. This is highlighted in the recent revision of the Graded Prognostic Assessment tool for patients with brain metastases, now adjusted to incorporate data for patients with NSCLC adenocarcinoma and ALK/EGFR mutations into the GPA existing tool, which was based on age, performance status, number of intracranial metastases and presence of extracranial metastases (9). Patients in the best prognostic category (including either an ALK rearrangement or EGFR mutation) had a median overall survival of 46 months. In the Magnuson study (4), further subgroup analysis was also carried out using the traditional GPA, comparing groups with unfavourable (0–1.5) to favourable (2–3.5) scores. The favourable outcome with SRS as upfront treatment was maintained in both groups. In the unfavourable group, median OS was 33 months (95% CI, 19–44) for those receiving upfront SRS compared with the cohorts who received upfront WBRT (27 months; 95% CI, 19–30) or EGFR-TKI (19 months; 95% CI, 17–25). In the favourable prognostic group, median OS was 64 months (95% CI, 46 to not reached) in the SRS cohort; compared with the cohorts who received upfront WBRT (52 months; 95% CI, 32–79) or those who received EGFR-TKI followed by RT at intracranial progression (32 months; 95% CI, 26–39).

The observed results in those who occupy the poorest prognostic group help to contextualize the management of this patient group in light of recent randomized data regarding the use of WBRT with and without EGFR-TKI therapy or compared to best supportive care. The recently reported QUARTZ trial demonstrated no survival difference between the WBRT or steroid/best supportive care arm in unselected, poor prognosis patients with NSCLC (10). Both the QUARTZ and the Magnuson studies defined survival duration from the same starting point, time of brain metastasis diagnosis. The median OS was only 8.5 and 9.2 weeks in WBRT and steroid/SBC arms of the QUARTZ trial, respectively, starkly contrasting with even the poorest cohort outcome in the Magnuson study (19 months for patients with a 0–1.5 GPA score who received upfront EGFR-TKI before salvage radiotherapy on intracranial progression). While roughly half of the patients in the QUARTZ study had adenocarcinoma, EGFR and ALK status was not collected/reported. Given this fact and the extremely poor survival noted in both arms, the relevance of this data to the typical EGFR mutated patient population with brain metastases seems tenuous at best.

The recently reported BRAIN trial (11) however, exclusively studied EGFR-mutated patients with at least three brain metastases. These patients were randomized to WBRT with or without chemotherapy or to the EGFR-TKI icotinib, with crossover to either arm allowed after disease progression. While it met its primary endpoint of improved intracranial PFS in the icotinib arm; 10.0 months (95% CI, 5.6–14.4) with icotinib versus 4.8 (2.4–7.2) months with WBRT, overall survival was not significantly different between the arms, 18.0 (15.1–20.9) months in the icotinib arm *vs.* 20.5 (17.0–24.1) months in the WBRT arm. Data on neurocognitive function was limited with no significant difference reported in the mini-mental status examination in 59 of the 176 accrued patients and quality of life was not collected. Given that the reported overall survival in the WBRT arm was lower than that observed in the Magnuson trial, this supports current widespread practice managing appropriate patients in this sub-group with upfront SRS, for the time being.

Physicians who treat patients in this field should buckle up however, further seismic upheavals are no doubt ahead. A randomized trial with osimertinib (12), an EGFR-

TKI with activity against T790M positive NSCLC and improved CNS penetration, has already shown improved PFS against second line chemotherapy on subgroup analysis in the 144/419 patients with brain metastases enrolled on study and phase 1 testing for another CNS active EGFR-TKI (AZD 9291) is ongoing in in patients with brain metastases and specific EGFR mutations (NCT02228369). The results of an ongoing phase 3 randomized study of SRS *vs.* WBRT (NCT01592968) for patients with 4 to 15 brain metastases—primary endpoints of neurocognitive function and intracranial control—will be awaited with great interest and potentially provide level 1 evidence to guide therapy in this patient population.

Until we have data from these studies and ultimately, studies comparing optimal, CNS-active EGFR-TKI therapy *vs.* SRS, upfront management with SRS where safe/feasible followed by EGFR-TKI with further SRS and/or WBRT for salvage (and judicious use of surgical resection for larger/symptomatic metastases) should remain the standard approach to management.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. May you live in interesting times. Available online: https://en.wikipedia.org/wiki/May_you_live_in_interesting_times
2. Sahgal A. Point/Counterpoint: Stereotactic radiosurgery without whole-brain radiation for patients with a limited number of brain metastases: the current standard of care? Neuro Oncol 2015;17:916-8.
3. Mehta MP. The controversy surrounding the use of whole-brain radiotherapy in brain metastases patients. Neuro Oncol 2015;17:919-23.
4. Magnuson WJ, Lester-Coll NH, Wu AJ, et al. Management of Brain Metastases in Tyrosine Kinase Inhibitor-Naïve Epidermal Growth Factor Receptor-Mutant Non-Small-Cell Lung Cancer: A Retrospective Multi-Institutional Analysis. J Clin Oncol 2017;35:1070-7.
5. Brown PD, Jaeckle K, Ballman KV, et al. Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial. JAMA 2016;316:401-9.
6. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol 2009;10:1037-44.
7. 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.
8. 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.
9. 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). JAMA Oncol 2017;3:827-31.
10. Mulvenna P, Nankivell M, Barton R, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. Lancet 2016;388:2004-14.
11. Yang JJ, Zhou C, Huang Y, et al. Icotinib versus whole-brain irradiation in patients with EGFR-mutant non-small-cell lung cancer and multiple brain metastases (BRAIN): a multicentre, phase 3, open-label, parallel, randomised controlled trial. Lancet Respir Med 2017;5:707-16.
12. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med 2017;376:629-40.

Cite this article as: Brade AM. The rapidly evolving treatment landscape for patients with brain metastases from epidermal growth factor receptor mutated non-small cell lung cancer. Transl Lung Cancer Res 2017;6(Suppl 1):S55-S57. doi: 10.21037/tlcr.2017.10.14

