Perspective

A new brainwave in non-small cell lung cancer: driving targeted therapy to central nervous system metastases

Luiz Henrique de Lima Araujo

Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Department of Internal Medicine, Division of Medical Oncology, The Ohio State University, Columbus, Ohio, USA

Corresponding to: Luiz Henrique de Lima Araujo, MD, MSc. Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Department of Internal Medicine, Division of Medical Oncology, The Ohio State University, Columbus, Ohio, US. Email: luiz.araujo@osumc.edu.

Submitted Jan 15, 2013. Accepted for publication Feb 20, 2013.
doi: 10.3978/j.issn.2218-676X.2013.02.03
Scan to your mobile device or view this article at: http://www.thetcr.org/article/view/965/html

Significant advances have been achieved in metastatic Non-Small Cell Lung Cancer (NSCLC) systemic therapy in the past decade (1,2). A landmark in this field was the discovery of sensitizing mutations in the epidermal growth factor receptor (EGFR) gene, and the realization that they could in fact predict responses to EGFR tyrosine kinase inhibitors (TKI) - erlotinib and gefitinib (1,2). However, the best approach to brain metastases (BM) is still a matter of debate, and was recently addressed in the provocative paper by Welsh *et al*. (3).

BM are a common feature in advanced NSCLC, affecting approximately 25% to 30% of cases (4). They are usually a therapeutic priority, and conventional systemic chemotherapy is traditionally ineffective in lesions within the central nervous system (CNS) (4). Selected patients with favorable performance status, limited number of brain lesions, and controlled extracranial disease may be offered surgical resection or stereotactic radiation surgery (SRS) (5,6). On the hand, whole brain radiation therapy (WBRT) is the standard option for patients with multiple BM, or when surgery or SRS are precluded. WBRT is associated with symptoms improvement, but the median survival is significantly poor, varying from 3 to 6 months (7).

In this context, Welsh *et al.* (3) published the results of a phase II trial evaluating the combination of erlotinib and concurrent WBRT in patients with BM from NSCLC. Their cohort comprised 40 patients enrolled between 2006 and 2010. Most patients were female (57%), white (72%), prior smokers (57%), and adenocarcinoma was the most frequent tumor histology (75%). Fifty-five percent had 4 or more BM, and 52% had received prior systemic chemotherapy. The median overall survival (OS) was 11.8 months, and the median CNS progression-free survival (PFS) was 8.0 months, which were significantly higher than results obtained in historic controls. Treatment was generally well tolerated, and erlotinib did not seem to increase neurologic deficits in comparison to historic data.

Several authors tried to improve the results of WBRT by combining it to different chemotherapy agents, including temozolomide (8-11). Despite the initial enthusiasm related to better response rates and acceptable toxicity, this strategy never proved to have a survival benefit (8-11). This might be explained by the fact that while temozolomide may have activity as a radiosensitizer, it lacks systemic activity in patients with NSCLC. On the other hand, erlotinib is an established systemic therapy in metastatic NSCLC (12), and also demonstrated activity as a radiosensitizer (13). These characteristics make erlotinib a very attractive agent to combine with WBRT in NSCLC, as explored by Welsh *et al*. (3).

The combination of erlotinib with standard WBRT was also evaluated in other studies (11,14,15). Lee *et al.* conducted a multicenter, randomized, phase II trial comparing the addition of erlotinib or placebo to WBRT in patients with NSCLC metastatic to the brain (TACTIC trial) (14). This study was halted early, after enrollment of the first 80 patients, and results should be released soon. In addition, a phase II study by Brustugun *et al.* is currently open for accrual in Norway (15), comparing WBRT with or without erlotinib, and is expected to enroll 150 patients. Sperduto *et al.* conducted a multicenter, phase III, North-American trial, comparing the addition of erlotinib or temozolomide to a WBRT plus SRS protocol (RTOG 0320) (11). One hundred twenty-six patients were accrued, all with 1 to 3 BM. In this

study, neither erlotinib nor temozolomide improved OS or CNS PFS. The median OS in the WBRT/SRS alone, with erlotinib, and with temozolomide were 13.4, 6.1 and 6.3 months, respectively. Similarly to the study by Welsh *et al.*, none of these trials selected patients based on the presence of EGFR mutations.

In the trial by Welsh *et al.* (3), 17 patients had known EGFR status, from which 9 (53%) had sensitizing EGFR mutations. Importantly, no evidence of increased toxicity was noted. Patients with EGFR mutations had longer OS (medians, 19.1 *vs.* 9.3 months) and CNS PFS (12.3 *vs.* 5.2 months) when compared to patients with wild-type tumors, although these differences were not statistically significant. These results underscore the importance of evaluating the outcomes of each aforementioned trial in the subsets with or without EGFR mutations before deciding for future clinical endeavors.

It is currently unclear whether the benefit of adding erlotinib would be due to its concomitant use with WBRT, to its systemic therapeutic effect *per se*, or both. This is a question that can only be answered by a randomized trial starting erlotinib concurrently or following WBRT in patients with EGFR mutated tumors. Erlotinib alone has consistently demonstrated a remarkable activity in patients with BM that have arisen from NSCLC harboring sensitizing EGFR mutations (16-19). In such circumstances, the response rate is over 70%, median PFS varies from 6.6 to 23.2 months, and OS ranges from 12.9 to 19.8 months (16-19). Hence, the erlotinib systemic effect (including its activity within the CNS) seems to be a key aspect of its benefit, and challenges the idea that its radiosensitizing effect is important at all. Indeed, EGFR TKIs alone have been considered a valid option to up-front WBRT for patients with asymptomatic BM harboring sensitizing EGFR mutations (20). In this case, patients should be closely monitored with brain imaging exams, and WBRT could be deferred until evidence of disease progression.

Some factors other than the addition of erlotinib to WBRT may have impacted the results obtained in the study by Welsh *et al.* (3), including a positive patient selection. In fact, EGFR mutations were present in 53% of tested tumors (3), and have been considered an independent prognostic factor in patients with BM (21). For instance, Eichler *et al.* (21) also found a higher survival from the time of BM among patients with EGFR mutations in a retrospective cohort comprising 93 patients (medians, 14.5 *vs.* 7.6 months). This finding was corroborated by multivariate analysis (HR 0.50, 95% CI, 0.30-0.82) (21). In their study, EGFR mutations were present in 44% of cases. It should also be acknowledged that erlotinib absorption and activation may be altered by a myriad of concurrent oral medications, including anticonvulsants and proton-pump inhibitors commonly used in patients with BM (22). Hence, the use of concomitant medications should be carefully monitored in trials evaluating patients with BM, and final analysis should take it into consideration alongside treatment compliance.

In summary, the study by Welsh *et al.* (3) highlights the discussion of novel therapeutic strategies in patients with BM from NSCLC, and meaningfully demonstrates a survival gain in comparison to historic controls based on WBRT. These intriguing results should be viewed in the context of upcoming results from other ongoing trials in order to confirm the benefits observed, with an especial interest for the correlative evaluations for subsets of patients with sensitizing EGFR mutations.

Acknowledgments

The author would like to thank David P. Carbone, MD PhD, for kindly reviewing this editorial, and Siow Ming Lee, PhD FRCP, Odd Terje Brustugun, MD PhD, and Paul W. Sperduto, MD MPP, for sharing their trials status.
Funding: None.

Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.3978/j.issn.2218-676X.2013.02.03). The author has no 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. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129-39.
2. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
3. Welsh JW, Komaki R, Amini A, et al. Phase II Trial of Erlotinib Plus Concurrent Whole-Brain Radiation Therapy for Patients With Brain Metastases From Non-Small-Cell Lung Cancer. J Clin Oncol 2013. [Epub ahead of print].
4. Langer CJ, Mehta MP. Current management of brain metastases, with a focus on systemic options. J Clin Oncol 2005;23:6207-19.
5. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 1990;322:494-500.
6. Suh JH. Stereotactic radiosurgery for the management of brain metastases. N Engl J Med 2010;362:1119-27.
7. 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.
8. Antonadou D, Paraskevaidis M, Sarris G, et al. Phase II randomized trial of temozolomide and concurrent radiotherapy in patients with brain metastases. J Clin Oncol 2002;20:3644-50.
9. Verger E, Gil M, Yaya R, et al. Temozolomide and concomitant whole brain radiotherapy in patients with brain metastases: a phase II randomized trial. Int J Radiat Oncol Biol Phys 2005;61:185-91.
10. Chinnaiyan P, Huang S, Vallabhaneni G, et al. Mechanisms of enhanced radiation response following epidermal growth factor receptor signaling inhibition by erlotinib (Tarceva). Cancer Res 2005;65:3328-35.
11. Sperduto PW, Wang M, Robins HI, et al. A Phase 3 Trial of Whole Brain Radiation Therapy and Stereotactic Radiosurgery Alone Versus WBRT and SRS With Temozolomide or Erlotinib for Non-Small Cell Lung Cancer and 1 to 3 Brain Metastases: Radiation Therapy Oncology Group 0320. Int J Radiat Oncol Biol Phys 2013. [Epub ahead of print].
12. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123-32.
13. Chinnaiyan P, Huang S, Vallabhaneni G, et al. Mechanisms of enhanced radiation response following epidermal growth factor receptor signaling inhibition by erlotinib (Tarceva). Cancer Res 2005;65:3328-35.
14. Clinicaltrials.gov. [Internet]. Bethesda (MD): National Cancer Institute. Available online: http://www.clinicaltrials.gov. Cancer Research, UK. ClinicalTrials.gov Identifier NCT00554775
15. Clinicaltrials.gov. [Internet]. Bethesda (MD): National Cancer Institute. Available online: http://www.clinicaltrials.gov. Cancer Research, UK. ClinicalTrials.gov Identifier NCT01518621
16. Porta R, Sánchez-Torres JM, Paz-Ares L, et al. Brain metastases from lung cancer responding to erlotinib: the importance of EGFR mutation. Eur Respir J 2011;37:624-31.
17. Kim KP, Lee DH, Lee J, et al. Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in non-small cell lung cancer patients harboring either exon 19 or 20 mutations. J Clin Oncol 2011;29:7606.
18. Wu YL, Zhou C, Cheng Y, et al. Erlotinib as 2nd-line treatment in advanced non-small-cell lung cancer (NSCLC) patients (pts) with asymptomatic brain metastases (BM) and its biomarker analysis - a phase 2 study (CTOMG0803). J Thorac Oncol 2001;6:S658.
19. de Lima Araújo LH, da Silveira JS, Baldotto CS, et al. Erlotinib in symptomatic brain metastases from a lung adenocarcinoma with a sensitizing EGFR mutation. J Thorac Oncol 2012;7:1059-60.
20. Jamal-Hanjani M, Spicer J. Epidermal growth factor receptor tyrosine kinase inhibitors in the treatment of epidermal growth factor receptor-mutant non-small cell lung cancer metastatic to the brain. Clin Cancer Res 2012;18:938-44.
21. Eichler AF, Kahle KT, Wang DL, et al. EGFR mutation status and survival after diagnosis of brain metastasis in nonsmall cell lung cancer. Neuro Oncol 2010;12:1193-9.
22. Cataldo VD, Gibbons DL, Pérez-Soler R, et al. Treatment of non-small-cell lung cancer with erlotinib or gefitinib. N Engl J Med 2011;364:947-55.

Cite this article as: de Lima Araujo LH. A new brainwave in non-small cell lung cancer: driving targeted therapy to central nervous system metastases. Transl Cancer Res 2013;2(1):51-53. doi: 10.3978/j.issn.2218-676X.2013.02.03