Editorial

Should optimal supportive care alone be the standard of care for brain metastases patients from non-small cell lung cancer, who are not eligible for radiosurgery or surgery?

May N. Tsao

Odette Cancer Centre, University of Toronto, Toronto, ON, Canada

Correspondence to: May N. Tsao, MD, FRCP(C). Odette Cancer Centre, University of Toronto, 2075 Bayview Ave., Toronto, ON, M4N 3M5, Canada. Email: may.tsao@sunnybrook.ca.

Comment on: 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.

Submitted Nov 05, 2016. Accepted for publication Nov 16, 2016.
doi: 10.21037/tcr.2016.12.03
View this article at: http://dx.doi.org/10.21037/tcr.2016.12.03

The Quality of Life after Treatment for Brain Metastases (QUARTZ) trial was a non-inferiority, phase III randomized trial comparing optimal supportive care (OSC) including dexamethasone versus OSC including dexamethasone and whole brain radiotherapy (WBRT). In this trial, 538 patients were recruited from 69 United Kingdom and three Australian centres. The primary outcome was quality-adjusted life-years (QALYs), generated from overall survival and patient completed EuroQOL EQ-5D questionnaires. The mean QALYs was 46.4 days for the OSC and WBRT arm versus 41.7 days for the OSC arm, with a mean difference of 4.7 days (90% CI: –12.7 to 3.3 days). In addition, there was no difference in overall survival (hazard ratio 1.06, 95% CI: 0.90–1.26), overall quality of life or dexamethasone use between the two groups (1).

The researchers for the QUARTZ trial are to be congratulated for formally examining and reporting the age old question as to whether WBRT adds benefit in terms of quality of life or survival. This multi-centre trial was well designed with excellent follow-up (90% of the expected follow-up forms were received and 80% expected quality of life forms completely filled). Only one patient was lost to follow-up (1).

Despite difficulties in accrual (2,3), the trial was ultimately successful in its completion and final publication. Why was accrual challenging? Perhaps the main reason is that management biases exist from the perspective of the patient/family and from the perspective of the treating medical team. Clinical equipoise may not exist for all eligible patients with respect to the QUARTZ trial.

Numerous studies have reported that palliative cancer patients have misconceptions regarding the intention of treatment and prognosis (4). Patients and families may expect treatment and it may be harder to accept that treatment may have little benefit (5-8). On the other hand, a patient who has very poor performance status may not want to return for daily brain radiation.

Physicians may also be biased. For patients with estimated good prognosis and/or quiescent extracranial disease, there may be reluctance in randomizing such patients to OSC. On the other hand, for patients with very poor performance status and uncontrolled extracranial disease, there may be reluctance in randomizing such patients to WBRT (9-11).

The challenges for participation in this trial may have also arisen because the overall concept of the QUARTZ trial goes against the grain of moving forward and testing innovative treatments.

The median survival in the QUARTZ trial was not statistically different between the two treatment arms: 9.2 weeks (95% CI: 7.2–11.1 weeks) for patients receiving OSC and WBRT versus 8.5 weeks (95% CI: 7.1–9.9 weeks) for patients receiving OSC alone. Due to poor survival, 53% of enrolled patients were assessed for quality of life at 4 weeks, 31% at 8 weeks only 18% were assessed at 12 weeks. It has been hypothesized that in patients with better survival, the benefit of WBRT (including reduction in steroid requirements) may occur more than 4 weeks after treatment. As such, the trial was criticized for the possibility that WBRT might benefit a subgroup of patients with better prognoses (12).

The QUARTZ trial did explore the effect of WBRT on different subgroups (1). For younger patients (age less than 60 years) WBRT may provide survival benefit. The median survival for patients younger than 60 years was 10.4 weeks (95 % CI: 6.3–13.4 weeks) for the WBRT and OSC arm versus 7.6 weeks (95% CI: 4.6–10.1 weeks) for the OSC arm, hazard ratio 1.48 (95% CI: 1.01–2.16). The p value for interaction between age group and treatment arm was 0.0061 (P=0.0043 with age as a linear trend). The association between KPS, P=0.0964 and primary non-small cell lung cancer (NSCLC) status (controlled or uncontrolled), P=0.0941 suggested a potential survival benefit with WBRT for patients with KPS of at least 70 and those with controlled NSCLC. A potential survival benefit with WBRT may also exist for better prognostic groups (P=0.0843 for RPA and P=0.0812 for GPA).

On the other hand, is there a subset of patients who are unlikely to benefit from WBRT and OSC and who may be better managed, instead, with OSC? The majority of patients in the QUARTZ trial (94%) were categorized into either Recursive Partitioning Analysis (RPA) class 2 or 3. Only 6% of enrolled patients were classified as good prognosis (RPA class 1). Furthermore, median survival for patients in the QUARTZ trial was disappointingly short. Median survival for those who received WBRT and OSC was 9.2 weeks (95% CI: 7.2–11.1 weeks) versus 8.5 weeks (95% CI: 7.1–9.9 weeks) for patients receiving OSC (1). As such, the QUARTZ trial provides evidence to support withholding WBRT and managing with palliative care alone for NSCLC brain metastases patients with poor performance status, progressive extracranial disease and anticipated survival of less than 3 months. There is debate as to whether OSC is the best management for better prognosis NSCLC brain metastases patients, who are not eligible for radiosurgery or surgery.

It is also important to note that the study period for accrual of patients in the QUARTZ trial was from March 2, 2007 to August 29, 2014. During this time, the benefit of molecular targeted therapy for certain NSCLC mutations emerged (13-24). Out of the 538 patients who were recruited into the QUARTZ trial, 36 received a tyrosine kinase inhibitor (1). Epidermal growth factor receptor (EGFR) mutated or anaplastic lymphoma kinase (ALK) rearranged molecular subtypes of NSCLC were not captured, due to the era in which the QUARTZ protocol was being developed. The QUARTZ trial was not designed to ascertain the role for WBRT, if any, in the present era of molecular targeted therapies for NSCLC patients (13-24).

The management of brain metastases is an example of personalized medicine where medical decisions are tailored to the individual. The evidence does not support a best supportive care alone approach for all brain metastases patients. Focal radiation (SRS, surgery, focal fractionated radiation) is also not supported by level I evidence for all brain metastases patients. Furthermore, there may be patients not represented by the QUARTZ trial who may benefit from WBRT.

The art of caring for these brain metastases patients takes into account the science learned from high quality trials and involves applying the therapeutic tools available (best supportive care including the use of dexamethasone, WBRT, SRS, surgery, alone or in combination). Management decisions are guided by risks of toxicity and takes into account prognosis with the goals to optimize survival, quality of life, neurocognition, and neurologic function.

While the QUARTZ trial illuminates the limitations of WBRT in certain subsets of NSCLC patients with brain metastases, the future of brain metastases management looks promising with respect to the development of new drugs and the advancement of radiation, surgical and imaging techniques.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by Section Editor Shaohua Cui (Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China).

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2016.12.03). 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. 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.
2. Langley RE, Stephens RJ, Nankivell M, et al. Interim data from the Medical Research Council QUARTZ Trial: does whole brain radiotherapy affect the survival and quality of life of patients with brain metastases from non-small cell lung cancer? Clin Oncol (R Coll Radiol) 2013;25:e23-30.
3. Fogarty M, Stephens R. QUARTZ trial: does WBRT bring any relief to patients with inoperable brain metastases? Oncology Times 2008;5:3.
4. Ghandourh WA. Palliative care in cancer: managing patients' expectations. J Med Radiat Sci 2016;63:242-57.
5. Chow E, Andersson L, Wong R, et al. Patients with advanced cancer: a survey of the understanding of their illness and expectations from palliative radiotherapy for symptomatic metastases. Clin Oncol (R Coll Radiol) 2001;13:204-8.
6. Chen AB, Cronin A, Weeks JC, et al. Expectations about the effectiveness of radiation therapy among patients with incurable lung cancer. J Clin Oncol 2013;31:2730-5.
7. Matsuyama R, Reddy S, Smith TJ. Why do patients choose chemotherapy near the end of life? A review of the perspective of those facing death from cancer. J Clin Oncol 2006;24:3490-6.
8. Weeks JC, Cook EF, O'Day SJ, et al. Relationship between cancer patients' predictions of prognosis and their treatment preferences. JAMA 1998;279:1709-14.
9. White N, Reid F, Harris A, et al. A Systematic Review of Predictions of Survival in Palliative Care: How Accurate Are Clinicians and Who Are the Experts? PLoS One 2016;11:e0161407.
10. Stephens RJ, Hopwood P, Girling DJ, et al. Randomized trials with quality of life endpoints: are doctors' ratings of patients' physical symptoms interchangeable with patients' self-ratings? Qual Life Res 1997;6:225-36.
11. Nieder C, Angelo K, Dalhaug A, et al. Palliative radiotherapy during the last month of life: Predictability for referring physicians and radiation oncologists. Oncol Lett 2015;10:3043-9.
12. Pechoux CL, Dhermain F, Besse B. Whole brain radiotherapy in patients with NSCLC and brain metastases. Lancet 2016;388:1960-2.
13. Chan BA, Hughes BG. Targeted therapy for non-small cell lung cancer: current standards and the promise of the future. Transl Lung Cancer Res 2015;4:36-54.
14. Kris MG, Natale RB, Herbst RS, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. JAMA 2003;290:2149-58.
15. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
16. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380-8.
17. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735-42.
18. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239-46.
19. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-34.
20. 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.
21. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 2005;366:1527-37.
22. Zhang I, Zaorsky NG, Palmer JD, et al. Targeting brain metastases in ALK-rearranged non-small-cell lung cancer. Lancet Oncol 2015;16:e510-21.
23. Chen Y, Yang J, Li X, et al. First-line epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor alone or with whole-brain radiotherapy for brain metastases in patients with EGFR-mutated lung adenocarcinoma. Cancer Sci 2016. [Epub ahead of print].
24. Khalifa J, Amini A, Popat S, et al. Brain Metastases from NSCLC: Radiation Therapy in the Era of Targeted Therapies. J Thorac Oncol 2016;11:1627-43.

Cite this article as: Tsao MN. Should optimal supportive care alone be the standard of care for brain metastases patients from non-small cell lung cancer, who are not eligible for radiosurgery or surgery? Transl Cancer Res 2016;5(Suppl 7):S1320-S1322. doi: 10.21037/tcr.2016.12.03

