Perspective

The practice-changing QUARTZ trial: is there any role for whole brain radiotherapy in patients with non-small cell lung cancer and brain metastases?

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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.

Abstract: Brain metastases (BM) remain a substantial source of morbidity and mortality in patients with lung cancer. Current clinical management of BM involves a combination of supportive care, brain radiotherapy and systemic treatment against the tumor. Whole brain radiotherapy (WBRT) has been a cornerstone in the treatment of BM for decades. Recently, the QUARTZ trial, a phase 3, non-inferiority, randomized clinical trial addressing the efficacy of best supportive care (BSC) alone or with WBRT in patients with NSCLC reported no differences in survival or quality of life between the two groups. In this perspective article, we will discuss the QUARTZ trial results and their implications for clinical practice. We will also discuss potential biomarkers that could be used to identify patients with radioresistance. This molecular approach might help, in addition to clinical variables, to define the patients that will obtain less benefit from WBRT and/or to design new targeted therapies to reverse radioresistance and improve the results of radiotherapy treatment when indicated.

Keywords: Lung cancer; whole brain radiotherapy (WBRT); QUARTZ; STAT3; silibinin; Id1; Id3

Submitted Dec 23, 2016. Accepted for publication Jan 11, 2017.
doi: 10.21037/tcr.2017.02.24
View this article at: http://dx.doi.org/10.21037/tcr.2017.02.24

Lung cancer is characterized by a high incidence of brain metastases (BM). Around 25–40% of patients with non-small cell lung cancer (NSCLC) will experience BM during the course of their disease (1) and approximately 10% of patients will present BM at first diagnosis of lung cancer (2). Lung cancers are the primary source of BM and account for 40–65% of secondary brain tumors (1,2). Patients who develop BM usually experience severe neurological symptoms and report a poor quality of life. Overall survival (OS) in patients with NSCLC and symptomatic BM is less than 3 months if left untreated, with most patients dying from neurologic causes (3).

The growing incidence of BM is in part attributed to the central nervous system being a sanctuary site due to the blood-brain barrier (BBB), which limits the activity of systemic therapies because therapeutic drug concentrations are not reached in central nervous system (4). This phenomenon limits the treatment options for these patients (2). Moreover, patients with BM are usually under-represented in clinical trials exploring the role of chemotherapy treatments. Therefore, prognosis of patients with NSCLC and BM is poor, with a median OS of 7 months (5), which is lower than the OS of the general population of patients with stage IV NSCLC.

Historically, treatment of BM has involved the combination of supportive treatment (corticosteroids for brain edema and antiepileptic drugs for seizures), whole brain radiotherapy (WBRT), and systemic treatment against the tumor (6). In selected patients, more radical treatments such as surgical approach and stereotactic radiosurgery (SRS) may be considered.

WBRT with doses up to 30 Gy is the standard of care for patients with >3 BM and good performance status [Karnofsky Performance Status (KPS) ≥70%] (4). Despite apparent efficacy of WBRT described initially in the decade 1950–1960, only one randomized clinical trial had been published in 1971 comparing supportive care alone or with WBRT (7). Though WBRT can induce objective responses, improving many neurological symptoms, enhancing quality of life, and prolonging survival, it can also cause acute and early delayed toxicity, with intense and irreversible late side effects that can have a profound effect on neurocognitive function and quality of life (8). Some efforts have been made to avoid or delay the use of WBRT to prevent this late toxicity. Most of the data of efficacy of WBRT for BM has been obtained from retrospective reviews of clinical series, where different prognostic subgroups of patients have been defined (5).

The QUARTZ randomized clinical trial has recently been reported (9). It is the only adequately powered phase 3, non-inferiority, randomized clinical trial addressing the efficacy of best supportive care (BSC) plus WBRT versus BSC alone in patients with NSCLC. The primary endpoint was quality-adjusted life-years (QALYs), while secondary outcomes included OS and quality of life. The authors of the study concluded that there is no difference in survival and quality of life between the two groups, which could suggest that WBRT has little effect in this clinical setting.

Despite this general conclusion, some limitations of the QUARTZ trial must be mentioned. Most of patients included were newly diagnosed with BM (88%); however it is much more common (3–4 fold more) that patients present BM during the evolution of the disease; therefore, there may have been a selection bias. Furthermore, patients included in the trial had a poor performance status (nearly 40% of patients had a KPS <70%). Indeed, as indicated in the study design, "clinicians were encouraged to approach potential participants about the trial if there was uncertainty in the clinicians' or patients' minds about the potential benefit of WBRT". This statement reflects the ethical aspect of the study, but may introduce a potential selection bias (patients that might benefit from WBRT were excluded). For these reasons, the general conclusion from the study should be interpreted with caution and not generalized to the clinical practice in the whole NSCLC population.

Interesting additional information can be obtained from the forest plot analysis of reported OS. According to this exploratory analysis, patients with poor KPS (<70%) had better OS when WBRT was not administered, while the opposite was observed in the group of KPS >70% who had better OS after receiving WBRT. Also, age seemed to be an important clinical variable, with significantly better results for patients younger than 60 years when they received WBRT. Therefore, the results of the QUARTZ trial most likely support the long-term data obtained from retrospective analysis of clinical practice where there was no clear benefit from WBRT in patients with poor performance status.

Another limitation of the study is that patients did not receive concomitant systemic treatment. A recent meta-analysis has shown that the combination of chemotherapy plus WBRT in patients with BM originating from NSCLC may increase treatment response rates of BM with limited toxicity (10). This could be explained by a greater infiltration of systemically administered drugs into brain tissue when radiation destroys the BBB. Along this line, in a phase II clinical trial published in 2013, cisplatin/pemetrexed concurrently with WBRT (30 Gy in 10 fractions) yielded a cerebral response rate of 68.3%, with an OS of 12.6 months in NSCLC (adenocarcinoma histology) patients with BM at presentation (11).

There is a strong need to identify novel treatment modalities to improve the high morbidity and mortality of patients with NSCLC and BM. The recruitment for the QUARTZ study covered 7 years, from 2007 to 2014. During this time, several new drugs have been incorporated into the treatment of advanced NSCLC patients, including targeted therapies against oncogenic driver mutations such as epidermal growth factor receptor (EGFR) activating mutations or rearranged echinoderm microtubule associated protein like 4-anaplastic lymphoma kinase (EML4-ALK).

In patients with NSCLC and BM harboring EGFR mutations, an impressive objective response rate of 82.4% has been described with erlotinib (12). Moreover, a complete brain response has been reported in patients receiving afatinib without WBRT (13). This constitutes a molecular subgroup of patients that can be treated initially with EGFR tyrosine kinase inhibitors (TKIs), with WBRT delayed until brain disease is uncontrolled. In patients with

EML4-ALK, crizotinib has some activity in BM, but better results have been obtained in central nervous system with 2nd and 3rd generation ALK TKIs (e.g., ceritinib, alectinib, and lorlatinib). In a recent published phase II trial, alectinib after crizotinib resistance has demonstrated activity for BM, with an overall response rate of 57% and with complete response in 20% of patients (14).

Similar to what is happening in medical oncology with the evolution to precision-based medicine; we should try to emulate this strategy with radiotherapy. An interesting approach could be to define biomarkers for radiotherapy efficacy. For example, expression of inhibitor of DNA binding 1 (Id1) may confer resistance to treatment, including radiotherapy (15). It has been reported that Id1 and Id3 co-expression seems to associate with poor clinical outcome in patients with locally advanced NSCLC treated with definitive chemoradiotherapy (16). Therefore, Id protein expression (or other biomarkers of radioresistance) could help to exclude patients who do not benefit from WBRT because of lack of efficacy, and prevent toxicity of the treatment.

Another interesting molecule is signal transducer and activator of transcription 3 (STAT3), which has been related to radioresistance in different cancer types (17,18). Studies have observed that STAT3 is involved in the generation of BM in preclinical models of several cancer types, including NSCLC. Our group has recently revised the evidence for silibinin, a natural polyphenolic flavonoid isolated from seed extracts of the herb milk thistle (*Silybum marianum*), and concluded that silibinin might be viewed as a natural inhibitor of active STAT3 (19). Moreover, we have recently reported that patients with NSCLC and BM resistant to chemotherapy and WBRT experienced a reduction of 70–85% in the volume of BM with the use of a silibinin-based nutraceutical (Legasil®, Mylan, Meda Pharma, Rottapharm-Madaus, Barcelona, Spain) (20).

In summary, there is still a place for WBRT in patients with NSCLC and BM. The QUARTZ trial confirms that WBRT should not be given to patient with KPS <70%. Finally, more studies are needed to identify the mechanisms of radioresistance, which will allow us to better select those patients who will not benefit from WBRT. Also, we need to develop new treatments that can increase the efficacy of WBRT in NSCLC patients with BM.

Acknowledgments

Funding: Dr. Joaquim Bosch-Barrera is supported by a Research Grant [2016] from the Spanish Society of Medical Oncology (SEOM, Madrid, Spain) and has received an Unrestricted Educational Research Grant from Meda Pharma (Germany).

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor San-Gang Wu (Department of Radiation Oncology, Xiamen Cancer Center, the First Affiliated Hospital of Xiamen University, Xiamen, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.02.24). The authors have no 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: Sais E, Menéndez JA, Bosch-Barrera J. The practice-changing QUARTZ trial: is there any role for whole brain radiotherapy in patients with non-small cell lung cancer and brain metastases? Transl Cancer Res 2017;6(Suppl 1):S201-S204. doi: 10.21037/tcr.2017.02.24

