

Erlotinib plus concurrent whole-brain radiation therapy for non-small cell lung cancers patients with multiple brain metastases

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Abstract: Sequencing of the epidermal growth factor receptor (*EGFR*) gene to identify mutations in lung adenocarcinomas is routine in clinical practice. The use of tyrosine kinase inhibitors (TKIs) has transformed the management of patients with brain metastases harboring *EGFR* mutations, with improved response rates (RR) and survival. We evaluate the role of concurrent TKI therapy and radiotherapy in this group of patients, considering this data in the context of emerging concepts in this advancing field.

Keywords: Brain metastasis; non-small cell lung cancer (NSCLC); whole brain radiotherapy (WBRT)

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Introduction

Patients with brain metastasis generally have a poor prognosis (1). Certain tumors including non-small cell lung cancers (NSCLC) have a particular predisposition to develop brain metastases (2). It has been estimated that up to 40% of patients with NSCLC cancer will develop metastasis to the brain during their disease trajectory (3). Historically progress in this field has been limited and treatments were mainly with steroid and whole brain radiotherapy (WBRT). The blood-brain barrier (BBB) is a challenging obstacle obstructing the delivery of drugs (4). Moreover, in the past patients with brain metastases have been excluded from clinical trials due to their poor prognosis and performance status (5).

Progress in genomic sequencing and the identification of actionable mutations has engendered the concept of personalized medicine. In NSCLC activating mutations in epidermal growth factor receptor (*EGFR*) (predominantly exon 19 and 21) are associated with oncogene addiction and tumor proliferation (6). First generation tyrosine kinase inhibitors (TKIs), erlotinib and gefitinib were developed to reversibly compete with the ATP-binding pocket of the *EGFR* kinase domain and demonstrate favorable responses in *EGFR* mutant tumors. In recent years, researchers have utilized TKIs to treat patients with brain metastasis (7-9).

Approaches adopted have included evaluating the role of TKIs alone or with the concurrent use of TKI inhibition and WBRT, in patients with brain metastases selected/unselected for *EGFR* mutation status.

In this commentary, we discuss the findings from Welsh *et al.* who published a study evaluating the role of concurrent erlotinib and WBRT in patients with brain metastasis originating from a NSCLC primary tumor. We review their findings and consider its role in the current context of the management of brain metastasis of NSCLC origin.

Concurrent WBRT and erlotinib

Welsh *et al.* undertook a phase II study enrolling 40 patients, using a historical data set as a control (10). Patients were recruited irrespective of their *EGFR* mutation status. In total 53% of patients recruited in the trial had received prior chemotherapy. In brief, patient characteristics included: 57.5% females, 75% adenocarcinomas, 72% white ethnicity, 27.5% of patients as never smokers and 45% of patients with 0–3 brain metastases. The treatment schedule consisted of a loading dose of erlotinib, 150 mg daily for 6 days, followed by concurrent WBRT and maintenance erlotinib until disease progression or discontinuation

due to intolerability. WBRT was administered at 2.5 Gy per day, 5 days per week up to a total dose of 35 Gy. The treatment was well tolerated, with no evidence of increased neurological toxicity compared to the historical data set. Welsh *et al.* reported a response rates (RR) of 86% and a median survival time of 11.8 months. The *EGFR* mutation status was available for 17 patients of which 53% of patients were *EGFR* mutant. Mutation status was determined directly from primary tumors. Analysis stratified by mutation status demonstrated a median survival time of 9.3 *vs.* 19.1 months in patients with *EGFR* wild-type and mutant status respectively. The 3-month central nervous system RR in wild-type *vs.* mutants' patients was 63% *vs.* 89% respectively.

Tactic study

The phase II tactic study was a randomized study evaluating the role of WBRT with concurrent erlotinib/placebo in patients with untreated brain metastases of NSCLC origin (11). In short, 80 patients were recruited and randomized to receive either erlotinib (150 mg) or placebo with concurrent WBRT followed by either maintenance erlotinib or placebo. The fractionation regimen used in this study consisted of 20 Gy in 5 fractions. Patients were selected with a radiation therapy oncology group recursive partitioning analysis of class I and II. There was no significant difference in neurological progression free survival (median 1.6 months in both arms $P=0.84$) or overall survival (2.9 *vs.* 3.4 months in placebo and erlotinib arms $P=0.83$). Of the 35 cases where the primary tumor was available, sequencing identified 2.9% *EGFR* mutations.

Reevaluation of the role of concurrent TKI and WBRT

The improved survival rates observed by Welsh *et al.* in comparison to the tactic study is likely to be mainly attributable to the increased *EGFR* mutation frequency in the former study (>50%). Despite the differing radiation fractionation schedules previous trials and a systematic review have failed to demonstrate a benefit in the duration of response and survival with radiation doses ranging from 20 Gy in 5 fractions to 50 Gy in 20 fractions (12-14).

Welsh *et al.* initiated their study prior to the approval of the use of TKIs in the first line setting. WBRT is associated with neurocognitive deficiencies in memory and dementia compelling clinicians to rethink the optimal

timing of WBRT (15-17). Currently in clinical practice TKIs (gefitinib, erlotinib and afatinib) are typically utilised in the first line setting to control intracranial metastasis delaying/obviating the need for WBRT. More recently Iuchi *et al.* have demonstrated that sequential usage of different TKIs can delay the administration of WBRT in *EGFR* mutants in a phase II study (9). The choice of TKI in the first line setting in the context of brain metastasis is unclear. Although studies evaluating the role of afatinib in this context are limited, the recent findings from Lux-Lung 7 demonstrated improved RR and duration of response favoring afatinib over gefitinib in systemic disease (18). The optimal schedule of TKI therapy is as yet undetermined. Researchers are exploring the role of sequential treatment with TKIs or high dose/pulsatile administration of a TKI (9,19,20). In parallel, the challenge for the pharmaceutical industry is to engineer newer generations of TKIs which are structurally smaller and lipophilic to increase penetrability of the BBB.

Clinical oncologists are reexamining the role of WBRT in controlling intracranial disease. The MRC Quartz trial is comparing WBRT and optimal supportive care (OSC) against OSC alone in inoperable brain metastasis of NSCLC origin of poorer performance status. An interim analysis demonstrated no detriment in quality of life or overall survival in the observation alone group (21). Efforts have been made to preserve memory and quality of life using hippocampal sparing radiotherapy (HSR) to preserve neural stem cells (22). The anticipated HIPPO trial (<https://clinicaltrials.gov/ct2/show/NCT02147028>) aims to compare HRS to conventional WBRT in preserving brain function in patients receiving radiotherapy following definitive treatment for brain metastasis. The findings from this study may influence whether HRS is routinely advocated in patients as the technique is time consuming and requires complex planning. The EORTC evaluated the role of WBRT following definitive surgery or stereotactic radiosurgery (SRS) in patients with oligometastatic brain metastasis (23). The addition of WBRT improved 2-year intracranial relapse rates (19% WBRT and SRS *vs.* 31% SRS alone and 27% with WBRT and surgery *vs.* 59% surgery alone). Despite the improved relapse rates observed with the addition of WBRT, this failed to translate to an improvement in overall survival. These findings support delaying the administration of WBRT in patients receiving definitive treatment for brain metastases, using MRI surveillance and salvage WBRT if required obviating neurocognitive toxicities.

Conclusions

In summation, there is very little evidence to support the use of WBRT and TKI to treat NSCLC patients with multiple brain metastases. For patients with *EGFR* mutation tumors, it is prudent to delay the administration of WBRT focusing on intracranial disease control with TKI therapy. This approach would postpone/obviate the neurocognitive toxicities associated with WBRT for many of these patients as median survival of these patients now double that of *EGFR* wild-type patients. Future advances for patients with *EGFR* mutation tumor and brain metastases may be driven by the development of newer generations of TKIs able to cross BBB, optimizing sequencing schedules and delaying radiotherapy strategies. A new prognostic index needs to be established for NSCLC patients developing brain metastases, which needs to take into account the oncogenic addicted tumors which may be associated with improved outcome when treated with TKIs alone.

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Footnote

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Comment on: 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;31:895-902.

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