

Cranial irradiation in patients with *EGFR*-mutant non-small cell lung cancer brain metastases

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Abstract: The most effective treatment approach for brain metastases in patients with non-small cell lung cancer (NSCLC) and activating epidermal growth factor receptor (*EGFR*) mutations is a current subject of investigation. Cranial irradiation is the standard treatment for brain metastases, but tyrosine kinase inhibitors (TKIs) such as erlotinib have also activity against brain metastases in this subset of patients. The combination of TKI and radiotherapy is a promising one, but data is lacking to indicate whether this is superior to erlotinib or whole brain radiation therapy (WBRT) alone. Retrospective data suggest that WBRT achieves more durable intracranial control compared to erlotinib alone. Randomized, prospective studies will be necessary to determine whether TKI, cranial irradiation, or both is the optimal initial treatment for brain metastases in *EGFR*-mutant NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor (*EGFR*); erlotinib; whole brain radiation therapy (WBRT)

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Brain metastases occur in 20% to 40% of patients with non-small cell lung cancer (NSCLC) (1). They are a common cause of morbidity and mortality and their incidence may be increasing (2). Historically, therapeutic options for brain metastases have been limited to local therapies such as whole brain radiation therapy (WBRT), stereotactic radiosurgery, surgery or a combination of the above. Due to concern for inadequate central nervous system (CNS) penetration, chemotherapy has not typically been considered a standard primary treatment for brain metastases. In a multi-institutional retrospective analysis that included 1,833 NSCLC patients with newly diagnosed brain metastases treated with radiation therapy between 1985 and 2007, a median overall survival of seven months (95% CI, 6.5–7.5 months) was reported (3).

It is now well established that NSCLC patients harboring activating epidermal growth factor receptor (*EGFR*) mutations have a different prognosis. Studies examining survival in *EGFR*-mutated patients have shown a more favorable median survival of 15–17 months from

onset of brain metastases (4,5). Based on randomized trials demonstrating improved survival, *EGFR* tyrosine kinase inhibitors (TKIs) have replaced cytotoxic chemotherapy as first-line treatments with patients with metastatic *EGFR*-mutant NSCLC (6,7). However, whether *EGFR*-TKI can enhance or replace cranial irradiation in the initial treatment of brain metastases remains unclear.

In 2013, Welsh *et al.* published the results of a bicentric phase II trial in the *Journal of Clinical Oncology* (8) that examined whether the combination of erlotinib and WBRT would improve median survival in patients with NSCLC brain metastases. Erlotinib is known to possess CNS penetrability (9). In the Welsh study, 40 NSCLC patients with radiographically confirmed brain metastases between 2006 and 2010 received a loading dose of erlotinib (150 mg per day for 6 days), followed by concurrent erlotinib (150 mg per day) with WBRT, followed by maintenance erlotinib (150 mg per day) until disease progression or adverse effects. WBRT was delivered as 30 Gy in 3 Gy fractions for the first 10 patients, then changed to a regimen of 35 Gy in

2.5 Gy fractions given concerns of possible neurotoxicity in two patients. The primary endpoint was to detect an increase in median survival from a historical control of 3.9 to 6.0 months. The authors reported that the combination of erlotinib and WBRT was well tolerated, with no grade 4 or 5 treatment-related toxicity. After median follow-up of 28.5 months, the median survival was 11.8 months, significantly surpassing the target of 6.0 months. Of the 40 patients included in the study, 17 had known *EGFR* status. Subgroup analysis showed a nonsignificant improvement in median survival (19.1 *vs.* 9.3 months, $P=0.53$) and CNS progression-free survival (12.3 *vs.* 5.2 months, $P=0.74$) in the nine patients with known activating *EGFR* mutations compared to the eight patients with known wild-type *EGFR*.

While this pioneering study demonstrates the safety and promise of administering concurrent erlotinib with WBRT, it does not directly indicate whether concurrent treatment is superior to either treatment alone (or in close succession) for *EGFR*-mutant patients. In preclinical models, overexpression of *EGFR* is associated with radiation resistance (10) and *EGFR* signaling blockade sensitizes *EGFR*-mutant cells to radiation (11). The investigators of the trial hypothesized that concurrent *EGFR* inhibition and WBRT may therefore be synergistic and potentially improve survival. However, the single-arm design of the study and the limited number of patients with known *EGFR* mutations leaves open the question of whether combination therapy would have been any more effective than erlotinib or WBRT alone. Though the study cohort's survival handily exceeded the historical expectation of 3.9 months, some of this could have been attributable to general improvements in the prognosis of NSCLC patients with brain metastases, due to factors such as stage migration from the widespread use of brain MRI screening. Known *EGFR*-mutant patients had particularly favorable results, but such patients are now known to have relatively better prognosis when treated with erlotinib alone.

There is prospective evidence that *EGFR*-TKIs are an effective primary treatment for *EGFR*-mutated NSCLC brain metastases. In an open-label, single institution phase II study, 28 molecularly selected patients with activating *EGFR*-mutant NSCLC and brain metastases received either oral gefitinib (250 mg daily) or erlotinib (150 mg daily) (5). Study patients did not receive prior local therapy for brain metastases such as radiation or surgery. The median survival and CNS progression-free-survival was 15.9 and 6.6 months, respectively. In another phase II trial, 40 patients

with non-molecularly-selected NSCLC and asymptomatic brain metastases were treated with erlotinib (150 mg daily). Clinically significant improvement in OS was observed in activating *EGFR* mutation-positive patients (37.5 months, $n=8$) compared to *EGFR* wild-type patients (18.4 months, $n=15$; $P=0.14$), as well as in CNS progression-free survival (15.2 *vs.* 4.4 months, $P=0.02$). These studies not only corroborate the longer survival observed for patients with *EGFR*-mutant NSCLC and brain metastases reported by Welsh *et al.*, they also suggest that erlotinib monotherapy may be an effective primary treatment for patients with *EGFR*-mutant NSCLC brain metastases.

There is no randomized data directly comparing erlotinib to WBRT for primary treatment of *EGFR*-mutant NSCLC brain metastases. In a retrospective analysis, our group examined the role of cranial irradiation in patients with *EGFR*-mutant lung adenocarcinoma and newly diagnosed brain metastases (12). While it did not reach statistical significance, we observed longer survival in patients who received WBRT ($n=32$, 35 months) compared to patients who received erlotinib alone ($n=63$, 26 months, $P=0.62$) for newly diagnosed brain metastases. Our results corroborate the favorable survivals reported by Welsh *et al.*, as well as the phase II studies of primary *EGFR*-TKI therapy for brain metastases discussed above. Furthermore, we found that patients who received WBRT had significantly longer time to intracranial progression compared to those who received erlotinib alone (24 *vs.* 16 months, $P=0.04$), despite having significantly greater intracranial disease burden (more patients with >3 brain metastases and larger lesions received WBRT). This study suggests that WBRT retains an important role in intracranial control in patients with *EGFR*-mutant NSCLC brain metastases. In a recent meta-analysis that included 12 non-comparative studies and 363 patients, upfront cranial radiation was found to improve intracranial disease control and survival outcomes compared to TKI alone (13). The majority of patients included in the study received TKI alone ($n=185$), 115 patients received WBRT alone, 23 patients received stereotactic radiosurgery alone, and 40 patients received concurrent WBRT and TKI. Despite significant methodological limitations, this analysis further highlights the notion that upfront radiotherapy should not be summarily abandoned in *EGFR*-mutant NSCLC patients even though targeted therapies have also demonstrated CNS activity.

Pre-clinical data has demonstrated that erlotinib can cause radiosensitization through cell cycle redistribution, induction of apoptosis, and inhibition of DNA repair (11). It

is therefore reasonable to hypothesize that the combination of erlotinib and WBRT for *EGFR*-mutant NSCLC would result in significantly improved CNS disease control and potentially enhance survival. In a retrospective analysis, Gow *et al.* demonstrated that patients with *EGFR* mutations had higher response rates to WBRT compared to patients with wild-type *EGFR* disease. The administration of *EGFR*-TKI during WBRT was independently associated with response to WBRT, and response to WBRT was an independent predictor for survival (14). In a second study, concomitant administration of gefitinib and WBRT was found to result in higher treatment response and disease control rates in patients with *EGFR*-mutant NSCLC brain metastases compared to gefitinib alone (15). In 2014, Lee *et al.* reported results of a multicenter trial that included 80 non-molecularly selected NSCLC patients with newly diagnosed brain metastases randomized to WBRT alone (20 Gy in 5 fractions) or WBRT with concurrent erlotinib (16). They reported median survival of 2.9 months with WBRT alone and 3.4 months with WBRT plus erlotinib. However, only one patient had known activating *EGFR*-mutation status, limiting the study's relevance to current practice where *EGFR* mutation status is routinely verified, and erlotinib is only offered to patients with activating mutations. Overall, these studies suggest that the approach of concurrent *EGFR*-TKI and WBRT is a promising treatment deserving further study in patients with brain metastases and *EGFR* mutations. However, definitive support for this strategy is limited by the dearth of prospective randomized data, and the fact that many published studies only contained a small subset of patients with known *EGFR* mutations.

In summary, the phase II study of concurrent erlotinib and WBRT from Welsh *et al.* demonstrates the tolerability and safety of the combination in treating newly diagnosed brain metastases from NSCLC. Patients with *EGFR*-mutated NSCLC brain metastases appear to have improved intracranial disease control and survival compared to patients with *EGFR* wild-type disease. Nevertheless, whether erlotinib, radiotherapy, or both is the optimal treatment for brain metastases in this population remains unanswered. Retrospective studies (12-14) indicate that upfront cranial irradiation may improve intracranial control and possibly survival compared to *EGFR*-TKI alone, and the combination of WBRT and *EGFR*-TKI may ultimately prove to be the best strategy (14,15). However, this needs to be confirmed with prospective randomized trials, one of which is ongoing: the TRACTS trial is comparing concurrent erlotinib and WBRT *vs.* erlotinib

alone (clinicaltrials.gov/NCT01763385). Crucially, this trial limits eligibility to patients with known activating *EGFR* mutations. Until such data are available, we suggest that patients with brain metastases from *EGFR*-mutant NSCLC should still be considered for upfront cranial irradiation, prior to or concurrent with erlotinib or other targeted therapies.

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Footnote

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Conflicts of Interest: The authors have no conflicts of interest to declare.

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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