The brain is one of the most common sites for lung adenocarcinoma metastasis, which are found in almost 20-30% of patients with the disease (1). These patients have poor median survival, and more effective therapies are urgently required. Since traditional chemotherapy is less effective against metastatic brain tumors, radiotherapy remains the main therapeutic or palliative option for inoperable central nervous system (CNS) disease. Radiotherapy supplemented with steroids has yielded responses rates of 50-75% for intracranial lesions, providing rapid attenuation of neurologic symptoms and improvement of performance status (2). However, brain metastases still herald a poor prognosis with a median survival of less than six months (3). Age, performance status, control of primary tumor, extend of extracranial disease, number of brain metastases, aggressive treatment modalities like surgery or radiosurgery, but also biomarkers such as expression levels of vascular enthothelial growth factor (VEGF), cyclooxygenase-2, epidermal growth factor receptor (EGFR) overexpression, and EGFR mutations have been explored as prognostic factors for patients with CNS metastases (4).

EGFR is a transmembrane protein with cytoplasmic kinase activity that can transduce growth factor signaling from the extracellular domain to the cell. Non-small cell lung cancer (NSCLC) patients with activating somatic mutations in the region of the EGFR gene that encodes the tyrosine kinase domain (such as mutations in exons 19 and 21) are highly responsive to EGFR-tyrosine kinase inhibitors (TKIs) and, as illustrated by individual trials and meta-analyses, EGFR TKIs can significantly improve progression-free survival compared with standard chemotherapy (5-7). It is also known that certain clinical or demographic characteristics, such as being Asian, female, a never smoker or adenocarcinoma or bronchioloalveolar carcinoma (BAC) tumor histology, are associated with a higher probability of response to EGFR TKIs (8).

The Journal of Clinical Oncology has featured recently the results of a multi-institutional phase II study of the EGFR inhibitor erlotinib with whole-brain radiation therapy (WBRT) for patients with brain metastases from a NSCLC primary disease (9). Forty NSCLC patients with brain metastases, regardless of EGFR status, received erlotinib monotherapy for one week, then concurrently with WBRT, followed by maintenance, a treatment which was feasible and tolerable and produced longer overall survival compared with historical controls, with particular benefit evident for patients with EGFR mutations (9). Overall response rate was 86% and at a median follow up of more than two years, median survival was 11.8 months, almost double the 6 months the study was designed to demonstrate (9). These results are impressive but require interpretation in the context of information which has become available since the enrollment of this trial began (7). Furthermore, the results of a recently published study indicate that patients with EGFR mutations may have prolonged survival after diagnosis of brain metastases, independent of treatment strategy (10). In recent years, there has been growing interest in the potential CNS activity of EGFR TKIs alone in NSCLC patients with EGFR activating mutations; the idea that erlotinib or
gefitinib may delay or obviate the need for brain radiation is appealing. However, the role of EGFR TKIs in the treatment of brain metastases remains unclear since data on the use of erlotinib or gefitinib are available from retrospective and non-randomized studies with a limited number of patients (Table 1).

In the study from Welsh et al. patients were enrolled regardless of EGFR status. Among 17 patients, for whom EGFR status was tested by DNA sequencing, median survival was 9.3 months for those with (WT) type EGFR and 19.1 months for those with EGFR mutations but this apparent difference was not statistically significant, highlighting the preferential activity of erlotinib in EGFR mutated tumors (9). However, more than 50% of patients who were tested for EGFR mutations had tumors with an EGFR activating mutation, a much higher percentage than what is normally expected from a random sample of NSCLC patients. It is possible that selection bias in this trial could explain this high percentage, since the trial demographics included younger age, a higher percentage of women and a higher percentage of never smokers than what is typical for patients with metastatic NSCLC (9). Therefore, the conclusions warrant further exploration before we can consider them indicative of EGFR mutated tumors having a CNS tropism.

In vitro studies have demonstrated the radiosensitivity of lung cancer cells with mutant EGFR (23). However, in the present study the authors emphasize in vitro data which demonstrate that EGFR TKIs can radiosensitize EGFR wild type tumors (24). Though overexpression of EGFR has been examined as a mechanism of resistance to radiotherapy, EGFR blockade has not been beneficial in tumors such as glioblastoma multiforme with increased expression of EGFR (25). Welsh et al. comment on the benefit of erlotinib and WBRT in EGFR WT and unknown status patients. However, this benefit still remains unclear without definite knowledge of the mutational status of the unknown group. It should also be borne in mind in this study the number of EGFR mutants was much higher than one would expect.

In conclusion, the trial conducted by Welsh et al. shows that the combination of erlotinib and WBRT is feasible, safe and effective. Though these results are provoking, they should be interpreted cautiously due to the small number

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Histology</th>
<th>Treatment</th>
<th>Response rate (CR+PR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceresoli et al. (11)</td>
<td>41</td>
<td>Mixed</td>
<td>Gefitinib</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Chiu et al. (12)</td>
<td>8</td>
<td>Mixed</td>
<td>Gefitinib</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Hotta et al. (13)</td>
<td>14</td>
<td>Adenocarcinoma</td>
<td>Gefitinib</td>
<td>6 (43%)</td>
</tr>
<tr>
<td>Wu et al. (14)</td>
<td>40</td>
<td>Adenocarcinoma</td>
<td>Gefitinib</td>
<td>15 (38%)</td>
</tr>
<tr>
<td>Kim et al. (15)</td>
<td>23</td>
<td>Adenocarcinoma</td>
<td>Erlotinib-gefitinib</td>
<td>17 (73%)</td>
</tr>
<tr>
<td>Porta et al. (16)</td>
<td>17</td>
<td>Adenocarcinoma (EGFR mutant)</td>
<td>Erlotinib</td>
<td>14 (82%)</td>
</tr>
<tr>
<td>Grommes et al. (17)</td>
<td>19</td>
<td>Adenocarcinoma (EGFR mutant)</td>
<td>Erlotinib</td>
<td>6 (67%)</td>
</tr>
<tr>
<td>Wu et al. (18)</td>
<td>48</td>
<td>Adenocarcinoma</td>
<td>Erlotinib</td>
<td>28 (58.3%)</td>
</tr>
<tr>
<td>Park et al. (19)</td>
<td>28</td>
<td>Adenocarcinoma (EGFR mutant)</td>
<td>Erlotinib-gefitinib</td>
<td>23 (83%)</td>
</tr>
<tr>
<td>Gow et al. (20)</td>
<td>63</td>
<td>Adenocarcinoma</td>
<td>Erlotinib with WBRT</td>
<td>29 (46%)</td>
</tr>
<tr>
<td>Bai et al. (21)</td>
<td>40</td>
<td>Adenocarcinoma</td>
<td>4 (10%) for intracranial disease 3 (7.5%) for extracranial disease</td>
<td></td>
</tr>
<tr>
<td>Lee et al. (22)</td>
<td>43 (30 EGFR mutated, 13 EGFR wt)</td>
<td>Adenocarcinoma</td>
<td>Erlotinib-gefitinib with WBRT</td>
<td>80 vs. 46% (P=0.037) (EGFR mutated vs. EGFR wt)</td>
</tr>
<tr>
<td>Welsh et al. (9)</td>
<td>40</td>
<td>Mixed</td>
<td>Erlotinib with WBRT</td>
<td>36 (86%)</td>
</tr>
</tbody>
</table>

EGFR, epidermal growth factor receptor; WBRT, whole brain radiation therapy; vs., versus; wt, wild type; CR, complete response; PR, partial response
of patients, lack of randomization and changes in the standard of care for patients with EGFR mutated tumors. Since erlotinib or gefitinib can be effective monotherapy for treatment of patients with EGFR activating mutations and brain metastases—as suggested by recent papers—the combination of EGFR TKIs and WBRT may be a reasonable option for the highly symptomatic subgroup of patients for whom it could be detrimental to wait for response to EGFR TKIs, or for those with numerous brain lesions that cannot be treated with stereotactic radiosurgery. Larger prospective randomized clinical trials that will confirm the role of EGFR TKIs in the response of brain metastases, alone or in combination with WBRT are awaited.

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References


