Significant advances have been achieved in metastatic Non-Small Cell Lung Cancer (NSCLC) systemic therapy in the past decade (1,2). A landmark in this field was the discovery of sensitizing mutations in the epidermal growth factor receptor (EGFR) gene, and the realization that they could in fact predict responses to EGFR tyrosine kinase inhibitors (TKI) - erlotinib and gefitinib (1,2). However, the best approach to brain metastases (BM) is still a matter of debate, and was recently addressed in the provocative paper by Welsh et al. (3).

BM are a common feature in advanced NSCLC, affecting approximately 25% to 30% of cases (4). They are usually a therapeutic priority, and conventional systemic chemotherapy is traditionally ineffective in lesions within the central nervous system (CNS) (4). Selected patients with favorable performance status, limited number of brain lesions, and controlled extracranial disease may be offered surgical resection or stereotactic radiation surgery (SRS) (5,6). On the hand, whole brain radiation therapy (WBRT) is the standard option for patients with multiple BM, or when surgery or SRS are precluded. WBRT is associated with symptoms improvement, but the median survival is significantly poor, varying from 3 to 6 months (7).

In this context, Welsh et al. (3) published the results of a phase II trial evaluating the combination of erlotinib and concurrent WBRT in patients with BM from NSCLC. Their cohort comprised 40 patients enrolled between 2006 and 2010. Most patients were female (57%), white (72%), prior smokers (57%), and adenocarcinoma was the most frequent tumor histology (75%). Fifty-five percent had 4 or more BM, and 52% had received prior systemic chemotherapy. The median overall survival (OS) was 11.8 months, and the median CNS progression-free survival (PFS) was 8.0 months, which were significantly higher than results obtained in historic controls. Treatment was generally well tolerated, and erlotinib did not seem to increase neurologic deficits in comparison to historic data.

Several authors tried to improve the results of WBRT by combining it to different chemotherapy agents, including temozolomide (8-11). Despite the initial enthusiasm related to better response rates and acceptable toxicity, this strategy never proved to have a survival benefit (8-11). This might be explained by the fact that while temozolomide may have activity as a radiosensitizer, it lacks systemic activity in patients with NSCLC. On the other hand, erlotinib is an established systemic therapy in metastatic NSCLC (12), and also demonstrated activity as a radiosensitizer (13). These characteristics make erlotinib a very attractive agent to combine with WBRT in NSCLC, as explored by Welsh et al. (3).

The combination of erlotinib with standard WBRT was also evaluated in other studies (11,14,15). Lee et al. conducted a multicenter, randomized, phase II trial comparing the addition of erlotinib or placebo to WBRT in patients with NSCLC metastatic to the brain (TACTIC trial) (14). This study was halted early, after enrollment of the first 80 patients, and results should be released soon. In addition, a phase II study by Brustugun et al. is currently open for accrual in Norway (15), comparing WBRT with or without erlotinib, and is expected to enroll 150 patients. Sperduto et al. conducted a multicenter, phase III, North-American trial, comparing the addition of erlotinib or temozolomide to a WBRT plus SRS protocol (RTOG 0320) (11). One hundred twenty-six patients were accrued, all with 1 to 3 BM. In this
study, neither erlotinib nor temozolomide improved OS or CNS PFS. The median OS in the WBRT/SRS alone, with erlotinib, and with temozolomide were 13.4, 6.1 and 6.3 months, respectively. Similarly to the study by Welsh et al., none of these trials selected patients based on the presence of EGFR mutations.

In the trial by Welsh et al. (3), 17 patients had known EGFR status, from which 9 (53%) had sensitizing EGFR mutations. Importantly, no evidence of increased toxicity was noted. Patients with EGFR mutations had longer OS (medians, 19.1 vs. 9.3 months) and CNS PFS (12.3 vs. 5.2 months) when compared to patients with wild-type tumors, although these differences were not statistically significant. These results underscore the importance of evaluating the outcomes of each aforementioned trial in the subsets with or without EGFR mutations before deciding for future clinical endeavors.

It is currently unclear whether the benefit of adding erlotinib would be due to its concomitant use with WBRT, to its systemic therapeutic effect *per se*, or both. This is a question that can only be answered by a randomized trial starting erlotinib concurrently or following WBRT in patients with EGFR mutated tumors. Erlotinib alone has consistently demonstrated a remarkable activity in patients with BM that have arisen from NSCLC harboring sensitizing EGFR mutations (16-19). In such circumstances, the response rate is over 70%, median PFS varies from 6.6 to 23.2 months, and OS ranges from 12.9 to 19.8 months (16-19). Hence, the erlotinib systemic effect (including its activity within the CNS) seems to be a key aspect of its benefit, and challenges the idea that its radiosensitizing effect is important at all. Indeed, EGFR TKIs alone have been considered a valid option to up-front WBRT for patients with asymptomatic BM harboring sensitizing EGFR mutations (20). In this case, patients should be closely monitored with brain imaging exams, and WBRT could be deferred until evidence of disease progression.

Some factors other than the addition of erlotinib to WBRT may have impacted the results obtained in the study by Welsh et al. (3), including a positive patient selection. In fact, EGFR mutations were present in 53% of tested tumors (3), and have been considered an independent prognostic factor in patients with BM (21). For instance, Eichler et al. (21) also found a higher survival from the time of BM among patients with EGFR mutations in a retrospective cohort comprising 93 patients (medians, 14.5 vs. 7.6 months). This finding was corroborated by multivariate analysis (HR 0.50, 95% CI, 0.30-0.82) (21). In their study, EGFR mutations were present in 44% of cases. It should also be acknowledged that erlotinib absorption and activation may be altered by a myriad of concurrent oral medications, including anticonvulsants and proton-pump inhibitors commonly used in patients with BM (22). Hence, the use of concomitant medications should be carefully monitored in trials evaluating patients with BM, and final analysis should take it into consideration alongside treatment compliance.

In summary, the study by Welsh et al. (3) highlights the discussion of novel therapeutic strategies in patients with BM from NSCLC, and meaningfully demonstrates a survival gain in comparison to historic controls based on WBRT. These intriguing results should be viewed in the context of upcoming results from other ongoing trials in order to confirm the benefits observed, with an especial interest for the correlative evaluations for subsets of patients with sensitizing EGFR mutations.

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