



# Upfront radiation versus EGFR-TKI: which is the best approach for EGFR-mutated NSCLC patients with brain metastasis?

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In *The Journal of Clinical Oncology*, William J. Magnuson (1) and colleagues have recently reported the results of a multicenter retrospective analysis comparing the impact of three different treatment strategies on survival outcomes of 351 patients with epidermal growth factor receptor (EGFR) mutated non-small cell lung cancer (NSCLC) and brain metastases (BM). Treatment options included stereotactic radiosurgery (SRS) followed by EGFR-TKI (n=100), whole-brain radiotherapy (WBRT) followed by EGFR-TKI (n=120), or EGFR-TKI followed by SRS or WBRT at the time of intracranial progression (n=131). Results showed a significantly longer median overall survival (OS) in patients who received upfront SRS (46 months) as compared to WBRT (30 months) or upfront TKI (25 months) (P<0.001), suggesting SRS followed by EGFR-TKI as the best treatment approach for these patients. The significant survival improvement was independent from significant prognostic covariables such as age, ECOG performance status, number of BM, *EGFR* mutation, and extracranial metastases, which were included in the multivariable analysis. The upfront use of radiotherapy resulted also in a significantly longer median time to intracranial progression (23 *vs.* 18 months; P=0.025) and 2-year OS rate (78% *vs.* 51%; P<0.001), and it was maintained regardless of patients' prognosis.

The results of several randomized phase III (2-9) studies convincingly and consistently demonstrated a significant superiority of upfront EGFR-TKI over platinum-based

chemotherapy for the subgroup of patients whose tumors harbor an EGFR activating mutation, leading to a paradigm shift in the first-line treatment of these patients, to whom the current gold standard is starting with an EGFR-TKI, gefitinib, erlotinib, or afatinib. However, several years later the approval of the first EGFR-TKI in the clinical setting the specific role of these agents in the therapeutic strategy of patients with BM remains still debated.

Brain metastases are a common event in EGFR-mutated NSCLC, with major negative impact on patients' quality of life (QoL) and survival, ranging from 4.5 to 11.0 months after the diagnosis (10,11). Despite the recent innovations in the treatments of EGFR positive NSCLC, current options available for EGFR-mutated patients with BM are very limited, also because of their historical low accrual in prospective clinical trials. Surgical resection, SRS or WBRT concomitantly or followed by EGFR-TKIs remain the most common approaches to treat these patients (12). However the optimal treatment sequences and combinations have not been clarified yet. Activity of upfront first-generation EGFR-TKIs has been reported in retrospective series including low number of East-Asian patients (13-16), overall showing encouraging intracranial response rates (RR) despite to the low penetration of such agents across the blood-brain barrier (BBB) (17,18). Some studies showed that erlotinib has a better central nervous system (CNS) penetration than gefitinib (19), thus suggesting it as preferred option for asymptomatic patients with BM.

Interestingly the second-generation EGFR-TKI afatinib has shown encouraging activity in NSCLC patients with BM (20). Gerber *et al.* retrospectively analyzed the survival outcomes of 222 patients with EGFR-positive NSCLC and newly diagnosed BM, showing no OS differences between WBRT and erlotinib, but a significant longer intracranial control in favour of the WBRT group (15). These data have been confirmed by a recent meta-analysis including 12 non-comparative trials and more than 300 EGFR-mutated NSCLC patients with BM revealing that WBRT improved both intracranial control and survival outcomes as compared to upfront EGFR-TKI monotherapy (21). Even if limited by methodological limitations, these studies underscored the important role of upfront WBRT in the management of BM, but didn't provide any evidences about SRS efficacy because of the very low number of patients treated with SRS in the included trials. In this scenario the study by Magnuson *et al.* (1) offered the opportunity to clarify a controversial and actual question: may radiotherapy be replaced by or deferred after upfront EGFR-TKI in patients with EGFR-positive NSCLC and BM? The results of this trial clearly demonstrated that deferring brain radiotherapy after EGFR-TKI led to inferior survival in the analyzed population, suggesting SRS followed by EGFR-TKI as the optimal treatment sequence for this subgroup of patients, regardless from significant prognostic factors. Furthermore the study addressed the controversy over the use of WBRT. Indeed the 120 patients who received WBRT followed by TKI reported a median survival of 30 months, which was significantly lower than the SRS-TKI sequence (45 months), even if they were more likely to have a less favorable prognosis. Since QoL is a relevant outcome for patients with metastatic disease, the use of SRS could allow patients to avoid the potential acute and late neurological toxicities associated with WBRT, often responsible for the patients' clinical decline. Unfortunately Magnuson *et al.* didn't collect adverse events (AEs), thus lacking a great opportunity to analyze both safety and QoL related to the different treatment strategies in a large real world population. Furthermore the results of this study should be cautiously interpreted because of the inherent methodological limitations. First the retrospective design of the study, even if partially corrected by the application of the propensity score analysis, may expose to significant selection biases, ultimately affecting the final results. Indeed the low percentage of patients with extracranial disease as well as the lower percentage of patients with stage IV assigned to the SRS arm, as compared to both WBRT and EGFR-TKI arms, could have influenced

the survival analysis in favour of upfront SRS. Furthermore the exclusion of patients who didn't receive EGFR-TKI after brain radiation or radiotherapy after TKI-failure could also have affected the survival analysis. Finally it's interesting to observe how medical oncologists considered upfront EGFR-TKI an effecting option for patients with asymptomatic disease, while WBRT was administered in patients with more than 5–10 BM who showed the strongest trend toward inferior OS, and SRS was preferred in patients with oligometastatic symptomatic disease. To summarize the study by Magnuson *et al.* (1) provide an interesting contribution to the current scientific debate supporting SRS as upfront treatment in the management of EGFR-positive NSCLC patients with BM. However, as declared by the authors, prospective randomized trials comparing these different strategies are urgently needed in order to definitively identify the optimal treatment approach for this subgroup of NSCLC patients. Recently the results of the first prospective randomized trial comparing EGFR-TKI icotinib *vs.* WBRT  $\pm$  chemotherapy in EGFR-mutated Asian NSCLC patients with BM, have shown a significant superiority of TKI in terms of both intracranial and systemic RR, as well as intracranial and systemic progression free survival (PFS), together with a lower incidence of severe treatment-related AEs (22). These data suggest icotinib as new standard 1-line treatment for EGFR-positive Asian patients with BM. However data on OS, neurotoxicity and secondary use of WBRT are not available yet. Furthermore it will be useful to see the results of other two ongoing randomized phase III trials comparing upfront EGFR-TKI erlotinib or gefitinib *vs.* WBRT (NCT02714010; NCT02338011) including also Caucasian population before to modify current treatment recommendations in the setting of patients. Besides these, randomized studies of SRS followed by EGFR-TKI *vs.* EGFR-TKI followed by SRS would be even more useful to clarify the optimal treatment sequence in this population. Concurrent administration of brain radiotherapy and EGFR-TKI could represent another promising approach allowing to combine the intracranial and the systemic control obtained with SRS and TKI, respectively. Pre-clinical data showed a synergistic effect between EGFR-inhibition and radiotherapy (23), likely due to the radio-sensitizing effect of TKIs and to the damage of BBB caused by radiation. Different phase II studies demonstrated a tolerable safety profile and encouraging activity of WBRT and EGFR-TKI combination in EGFR-positive NSCLC patients with BM (24,25). The prospective randomized TRACTS study (NCT01763385) is currently

investigating WBRT plus erlotinib combination *vs.* erlotinib alone in this subset of patients, and results are eagerly awaited. As regards new treatment options, encouraging data emerged from the phase I BLOOM study including EGFR-mutated NSCLC patients progressed on prior treatment with EGFR-TKI with a confirmed diagnosis of BM. Among the 21 patients receiving osimertinib 160 mg daily, 33% had partial response (PR) and 43% had stable disease (SD), with a tolerable safety profile including only 14% grade  $\geq 3$  drug-related AEs (26). Waiting for the results in the T790M-positive cohort, osimertinib has already shown high activity in patients with CNS disease harboring T790M mutation enrolled in two phase II studies (26), likely due to its greater penetration of animal models' BBB compared to other TKIs, gefitinib, rociletinib, or afatinib (27). Furthermore the recent results of the AURA3 trial demonstrated a significant survival benefit of osimertinib over platinum-chemotherapy in 144 T790M-positive patients with CNS metastasis at baseline, suggesting it as a very effective option in this population (28).

In conclusion the study of Magnuson *et al.* represents a significant attempt to improve the management of EGFR-mutated NSCLC patients with BM. However, as mentioned before, such results should be interpreted taking into account the new treatment options such as third-generation TKI which will be early available for these patients. Finally, the results of prospective ongoing randomized trials will be crucial to define the optimal treatment approach for each patient with EGFR-positive NSCLC and BM.

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