



How upfront can we be about upfront therapy for brain metastases in patients with activating epidermal growth factor receptor mutation?

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Molecular-targeted therapy has already changed the paradigm of cancer therapy. Among many molecular-targeted therapeutic agents, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) have significantly improved the outcomes of lung cancer patients with EGFR activating mutations and become the standard therapy as first-line or front-line therapy for them. On the other hand, advance in high-technology radiotherapy, such as stereotactic radiosurgery (SRS), has dramatically improved our capability of local control of small tumors with reduction in toxicity compared to conventional radiotherapy. Owing to the advances, we sometimes have to face a big dilemma when choosing front-line therapy for patient with both activating EGFR mutation and brain metastasis simultaneously. To make matter worse, as more sensitive brain imaging or magnetic resonance imaging (MRI) of the brain has already become a routine staging scan in advanced or metastatic non-small cell lung cancer (NSCLC), we see metastatic brain tumors more often than before and most of them are very small or asymptomatic.

Recently, Magnuson *et al.* published a multi-institutional but retrospective analysis comparing outcomes for patients with EGFR mutation and brain metastases (1). In the study, out of 351 patients from six institutions, 131 (37%) received upfront EGFR-TKI therapy followed by SRS or whole-brain radiotherapy (WBRT) at intracranial progression while another 120 (34%) received WBRT followed by

EGFR-TKI therapy and the other 100 (29%) received SRS followed by EGFR-TKI therapy. As a result, the median overall survival (OS) for upfront EGFR-TKI, WBRT and SRS cohorts was 25, 30 and 46 months, respectively ($P < 0.001$). Of note, on multivariable analysis, SRS *vs.* EGFR-TKI and WBRT *vs.* EGFR-TKI were independently associated with improved OS [hazard ratios (HR) 0.39, 95% confidence interval (CI), 0.26–0.58, $P < 0.001$ and HR 0.70, 95% CI, 0.50–0.98, $P = 0.039$, respectively]. It is suggested that upfront radiotherapy to brain, especially SRS, should be used in this clinical setting. However, we must be very cautious when interpreting the results. As mentioned by the authors, the study is retrospective and has inevitable biases. First of all, patients who failed to receive EGFR-TKI therapy after WBRT or SRS, failed to receive radiotherapy after intracranial progression on EGFR-TKI and were missing covariable were excluded from the study. Patients undergoing surgical resection were also excluded. In our prior studies, a significant portion of patients who had both EGFR mutation and brain metastases but received upfront EGFR-TKI therapy did not have to receive local therapy to the brain during their disease course owing to durable disease control or rapid progression of extracranial disease rather than intracranial disease (2,3). On the other hand, some of patients with initially good performance status did not receive further chemotherapy due to early death or deterioration of performance after frontline WBRT (4).

Including patients who failed to receive EGFR-TKI therapy after upfront radiotherapy or those who received upfront EGFR-TKI therapy due to being not eligible for upfront radiotherapy at baseline might be more confusing in analysis or interpretation. In this regard, prospective clinical trials are warranted, but they seem not feasible in the near future because of the rapid advance in systemic therapy as well as the enormous heterogeneity of brain metastases in terms of size, number and nature.

As mentioned, we have to consider newly developed agents in clinical use and clinical trials, some of which, such as osimertinib and AZD3759, are well known to penetrate well into the brain or cross the blood brain barrier (5-7). The AURA3 trial, comparing osimertinib with standard platinum doublet chemotherapy after failure of EGFR-TKI therapy, showed that osimertinib improved significantly progression-free survival (PFS) in patients with brain metastasis at baseline (34% of all patients, 8.5 *vs.* 4.2 months, HR 0.32, 95% CI, 0.21–0.49) as well as in all patients (10.1 *vs.* 4.4 months, HR 0.30, 95% CI, 0.23–0.41) (5). It is suggested that after failure of the 1st- or 2nd-generation EGFR-TKI therapy, the 3rd-generation EGFR TKIs be an option as salvage therapy for brain metastasis. In addition, the 3rd-generation EGFR TKIs are now being tested as frontline-therapy including FLAURA study of osimertinib (NCT 02296125) based on a prior promising result of phase I expansion study, in which osimertinib showed longer PFS as first-line therapy (8). Immune checkpoint inhibitors, which are now changing the paradigm in cancer therapy, should not be overlooked as well. Disappointedly, these have not shown a good activity in patients with EGFR mutation yet. However, ipilimumab and nivolumab combination was suggested to be active for patients with EGFR mutation and pembrolizumab showed strong concordance between intracranial and systemic responses (9,10). Therefore, we can hardly recommend prospective clinical trials, especially randomized ones using rather old EGFR TKIs. Instead, other types of studies such as comparative effective research might be more appropriate. And when additionally considering the heterogeneity of metastatic brain tumors, multidisciplinary approach including surgery, radiotherapy, systemic therapy and even experimental therapy, might be more required for the time being.

Regarding multidisciplinary approach, we should take into account of not only survival but also quality of life (QOL) including neurocognitive function. In the literature, adjuvant WBRT after surgery or radiosurgery was reported

to negatively impact some aspects of health-related QOL (HRQOL) even if these effects are transitory, and neurocognitive function as well (11,12). A wide spectrum of neurocognitive impairment related to WBRT has been described well from the most severe, overt dementia to just decline in memory, concentration or executive function. Although it is a very old study, the incidence of dementia was reportedly 1.9–5.1% and the patients at risk included high-fractional, doses, concurrent chemotherapy and, of note, survival of more than 1 year (13). Mild neurological impairment is known detectable in the majority of patients receiving WBRT and its prevalence increases with time. Related to SRS, symptomatic radiation necrosis, a well-known serious long-term complication ranging from focal neurologic deficit to loss of patient autonomy, is now being reported increasingly, accounting for about 2% to 32% (14).

The results from many studies cannot be easily interpreted and adopted in real clinical practice due to many reasons including not only methodological flaws of and inconsistencies between the trials but also heterogeneity of both patients and tumors in the trials. Of course, we need more studies of novel systemic approaches with or without local modalities including surgery or radiotherapy, which should evaluate HRQOL and neurocognitive function as well. However, the optimal management requires a multidisciplinary approach accounting for individual characteristics of both patient and tumor.

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Footnote

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