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Letter to the Editor

Erlotinib or Radiotherapy in the Treatment of Brain Metastasis from EGRF-Mutant NSCLC?

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Dear Editor,

Mutations in the epidermal growth factor receptor (EGFR) are common in non-small cell lung cancer (NSCLC). Tyrosine kinase inhibitors (TKIs) are the mainstay of the treatment of patients with EGFR mutations. By inhibiting phosphorylation of intracellular domain of the EGFR, TKIs disrupt signal transduction in the ras/eaf/MAPK and PI3K/Akt pathways, which are known to play important roles in cell growth and proliferation, angiogenesis, tumor invasion, and metastasis. In non-selected patients with NSCLC, TKIs achieved a 10% response in the EGFR. Thus, patient populations who benefited from these agents were investigated, and high response rates and long survival times were achieved with both first- and second-line therapies in specific subgroups [1-3].

The rapid division and adaptation of cancer cells to all conditions cannot generally be overcome with therapies directed toward a single target, and resistance may develop against novel agents within the short term. Blocking signal transduction in a signaling pathway may lead to compensatory activation of other signaling pathways. The response rate of TKIs is 75% in patients with EGFR-mutant tumors while 25% of patients do not respond this therapy [4]. Resistance then develops within 6 months and progression re-emerges in the former patient group. Although EGFR is an appropriate mutation for TKIs to act upon, lung cancers show de novo resistance against them. In other words, the presence of mutations except somatic EGFR mutations in k-ras, b-raf, PIK3CA, and T790M–which are involved in signal transduction and MET amplification–may attenuate the effectiveness of TKIs [5].

After demonstrating that EGFR-TKI may enhance the anti-tumor activity of ionizing radiation in preclinical studies, studies have emerged investigating TKI as monotherapy and in combination with radiotherapy in EGFR-mutant NSCLC and brain metastasis. Zhang et al. [3]. evaluated the effectiveness of erlotinib in patients with EGFR-mutant NSCLC and brain metastasis, reporting a response rate of 57% and a disease control rate of 91%. The authors found the median progression-free survival to be 9.3 months and reported that there was no significant difference in overall survival between patients receiving and those not receiving radiotherapy to the brain [3]. In a phase I study, oral erlotinib therapy with pulse/continuous doses was well tolerated in patients with EGFR-mutant NSCLC and brain metastasis with response and overall response rates of 75% and 74%, respectively [1]. In another study, stereotactic radiation therapy (SRS), whole brain radiotherapy (WBRT), and TKI therapy were compared in terms of their effectiveness and safety in cranial metastasis from EGFR-mutant NSCLC. The study included 351 patients who were randomized to receive SRS or WBRT followed by TKI or TKI followed by SRS or WBRT. The response rate, time to progression, and median survival time increased significantly in patients treated with SRS followed by TKI [2]. Furthermore, the incidence of neurocognitive disorder was significantly lower in the same group when compared with those that received WBRT [2]. A meta-analysis by Zheng et al. [6] reported that adding gefitinib/erlotinib therapy to WBRT resulted in a significant increase in the overall and disease-free survival in patients with brain metastasis from EGFR-mutant NSCLC when compared to those that received WBRT alone. Ulahannan et al. [7] reported that WBRT plus TKI therapy may increase neurocognitive disorder in multiple brain metastases from NSCLC and recommended delaying WBRT if brain metastasis could be controlled by TKIs.

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In recent years, there have been significant advances in the treatment of cranial metastasis from EGFR-mutant NSCLC. However, optimal therapy is still considered a field requiring further studies. TKI is not as sufficient as a monotherapy, possibly owing to resistance and the ongoing activation of signaling pathways shared by distinct growth factors. Thus, it will be helpful to investigate effects of sequential use of TKIs with SRS on response and survival. Currently, it is apparent that there is a need for larger studies that may serve as guides to determine an optimal treatment strategy when using TKIs in combination with radiotherapy.

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