Editorial

Efficacy of erlotinib plus concurrent whole-brain radiation therapy for patients with brain metastases from non-small cell lung cancer

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Abstract: Treatment and control of brain metastases are important in patients with non-small cell lung cancer (NSCLC). Whole brain radiation therapy (WBRT) has a major role in the management of brain metastasis. Recently, efficacy erlotinib plus concurrent WBRT for patients with brain metastases from NSCLC was reported. Herein, we discussed the results and commented the clinical matters in future.

Key Words: EGFR-TKI; stereotactic radiosurgery; EGFR mutation

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Lung cancer is the leading cause of cancer mortality worldwide and also the most common origin of brain metastases, accounting for 40-50% during the clinical course of lung cancer (1). Non-small cell lung cancer (NSCLC) represents 85-90% of all lung cancers. Brain metastases are one of the more debilitating effects of NSCLC because even small lesions can significantly affect morbidity and mortality. Whole brain radiation therapy (WBRT) has a major role in the management of brain metastasis; however, the survival of most patients with brain metastasis remains limited. Radiotherapy prolongs median survival to 3-8 months, but the median survival time after WBRT correlated strongly with the patient's age, performance score, and number and location of metastatic lesions (2,3). In addition, it is well known that improved local control of brain lesions does not guarantee the improved survival of patients with a short life expectancy, due to the progression of extracranial disease. Thus, a new development of further treatment options or strategies for brain metastases in patients with NSCLC is eagerly awaited.

Welsh *et al*. (4) tested a phase II clinical trial of erlotinib, a tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR), and concurrent WBRT for patients with brain metastases from NSCLC. The main evaluating points were the survival time, radiological response and safety. Forty patients were enrolled and completed erlotinib plus WBRT (median age, 59 years). The overall response rate in the brain lesions was 86% (n=36). No increase in neurotoxicity was detected, and no patient experienced grade ≥4 toxicity, but three patients required dose reduction for grade 3 skin rash. At a median follow-up of 28.5 months (for living patients), median survival time was 11.8 months (95% CI, 7.4 to 19.1 months). The survival was almost double the 6 months estimated by the historical data (5,6) and median Diagnosis-Specific Graded Prognostic assessment score (7). They concluded that erlotinib was well tolerated in combination with WBRT, with a favorable objective response rate. In addition, it is well known that the efficacy of erlotinib is strongly associated with *EGFR*-sensitive mutation status in NSCLC (8). Almost half of patients had sensitive *EGFR* mutations in their study and median survival time was 9.3 months for those with wild-type *EGFR* and 19.1 months for those with *EGFR* mutations.

It has been suggested that *EGFR* mutations confer radiosensitivity *in vitro* (9). Gow *et al*. (10) demonstrated that the presence of *EGFR* mutations is an independent predictor of response to WBRT in brain metastases of lung adenocarcinoma. In addition, several preclinical data demonstrated a favorable antitumor interaction between

EGFR inhibitory agents and radiation (11-13). Although the potential relationship and/or synergic effects in the brain remain unclear, the present study shows that the combination with erlotinib and WBRT to treat brain metastases in patients with NSCLC is a promising strategy. It has been shown that radiation damages endothelial cells and results in increased permeability of the blood-brain barrier (14). Theoretically, erlotinib concentration in the brain might increase during WBRT. Togashi *et al*. (15) measured erlotinib concentrations in plasma and cerebrospinal fluid (CSF) in NSCLC patients with brain metastases. The CSF penetration rates of erlotinib were 5.1%±1.9%, which exceeded its median inhibitory concentration (IC50) in intact tumor cells that expressed wild-type epidermal growth factor receptor. Furthermore, the CSF concentration of erlotinib is higher than that of other EGFR-tyrosine kinase inhibitors (16,17). Thus, WBRT and erlotinib might enhance therapeutic effects each other in patients with brain metastasis.

Welsh *et al*. (4) commented the limitations of their study. First, the study was performed by too small numbers and lack of randomization. In addition, there is bias with regards to number of brain lesions, patient age, patient performance status, etc. Second, WBRT was used in the study. Recently, stereotactic radiosurgery (SRS) has become a widely used treatment modality for brain metastases, in particular, in patients with a small number (1 to 3) of brain lesions. Kong *et al*. (18) reported the clinical outcomes of patients with synchronous brain metastases from NSCLC who were treated with gamma knife radiosurgery. The median survival time for this series was 12 months from the diagnosis. In addition, they described that subsequent chemotherapy and WBRT were significant predictors for prolonged survival. On the other hand, we have actually experienced certain cases of brain metastases from NSCLC who were treated with only SRS without subsequent WBRT and resulted in good local control in the brain. Furthermore, we have an unsettled matter from the results of Welsh's study. Porta *et al*. (19) demonstrated that only erlotinib without WBRT was usefulness for the metastatic brain tumor in patients with sensitive *EGFR* mutation. Based on the result, *EGFR* mutated patients with brain metastases could be treated initially with erlotinib. The omission of WBRT might be capable in certain cases whose brain lesions successfully responded to erlotinib. Thus, induction of WBRT might be depended to the response to initial therapy of erlotinib in patients with *EGFR* mutated NSCLC. Concurrent or sequential WBRT with erlotinib, which is better in *EGFR* mutated NSCLC patients with brain metastases? Taken together, additional clinical trials are necessary to confirm the radiosensitizing effects of WBRT concurrent with erlotinib therapy and should be compared with the clinical data obtained by SRS approach or the influence of erlotinib treatment schedule on survival.

Finally, Welsh *et al*. (4) described that *EGFR* mutations may be more prone to brain metastases than patients with non-mutated tumors, because almost half of the enrolled subjects were positive for *EGFR* mutations. However, *EGFR*-status was analyzed retrospectively and the number was too small to evaluate the frequency of *EGFR*-mutation.

In conclusion, although many issues remain to be addressed, we believe that with additional fundamental research and clinical trials, the combination with erlotinib and WBRT to treat brain metastases in patients with NSCLC will be a promising strategy.

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