

Case Report

A study on Erlotinib metabolism of phenytoin

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Seizure is a common manifestation of advanced non-small cell lung cancer (NSCLC) associated with brain metastasis. Anticonvulsants are usually required in addition to brain irradiation therapy for disease control. Concurrent chemotherapy or target therapy might have drug interactions with anticonvulsants and alter the effectiveness of such drugs. Such drug interactions are rarely recognized in clinical practice. We report a case with NSCLC complicated with brain metastasis in which the initiation of erlotinib treatment resulted in recurrence of seizure due to a decreased blood phenytoin level.

Key words: Erlotinib, anticonvulsant, brain metastasis, phenytoin, non-small cell lung cancer.

INTRODUCTION

Brain metastasis occurs frequently in patients with advanced non-small cell lung cancer (NSCLC). Among this group of patients, seizure is a common manifestation which requires the symptomatic treatment with anticonvulsants in addition to brain irradiation therapy. Concurrent chemotherapy is usually administered for the disease control. Apart from chemotherapy, treatment with target therapy agent such as erlotinib which inhibits epidermal growth factor receptor (EGFR) has also been shown to benefit patients with NSCLC including prolonging the survival (Shepherd et al., 2005). Nevertheless; chemotherapeutic drugs or target therapy agents might have drug interactions with anticonvulsants and possibly alter their effectiveness (Vecht et al., 2003). Until recently, there have been limited reports regarding such drug interactions, particularly between target therapy agents and anticonvulsants. Chhun and colleagues showed that the administration of phenytoin decreased serum level of gefitinib, another target therapy agent used in NSCLC treatment (Chhun et al., 2009). On

the other hand, Grenader reported a case whose phenytoin level was elevated by erlotinib (Grenader et al., 2007). Here we report a case in which the initiation of erlotinib treatment resulted in recurrence of seizure due to a decreased phenytoin level. This finding is opposite to Grenader's report.

CASE REPORT

The patient was a 63-year-old man with the initial presentation of a new-onset of right hemiplegia followed by generalized convulsion (tonic-clonic seizure). Phenytoin was administered immediately with an intravenous loading dose of 750 mg followed by a maintenance dose of 300 mg orally per day. After stabilization of convulsion, the brain computerized tomography (CT) revealed cerebral tumors with multifocal edema and ventricle compression (Figure 1A). Thoracic images including a chest CT were performed under the impression of metastatic lung cancer, which showed a pulmonary tumor over left upper lobe (Figure 2). Pulmonary adenocarcinoma was proved through taking a subsequent bronchoscopic biopsy.

Chemotherapy with gemcitabine plus cisplatin was

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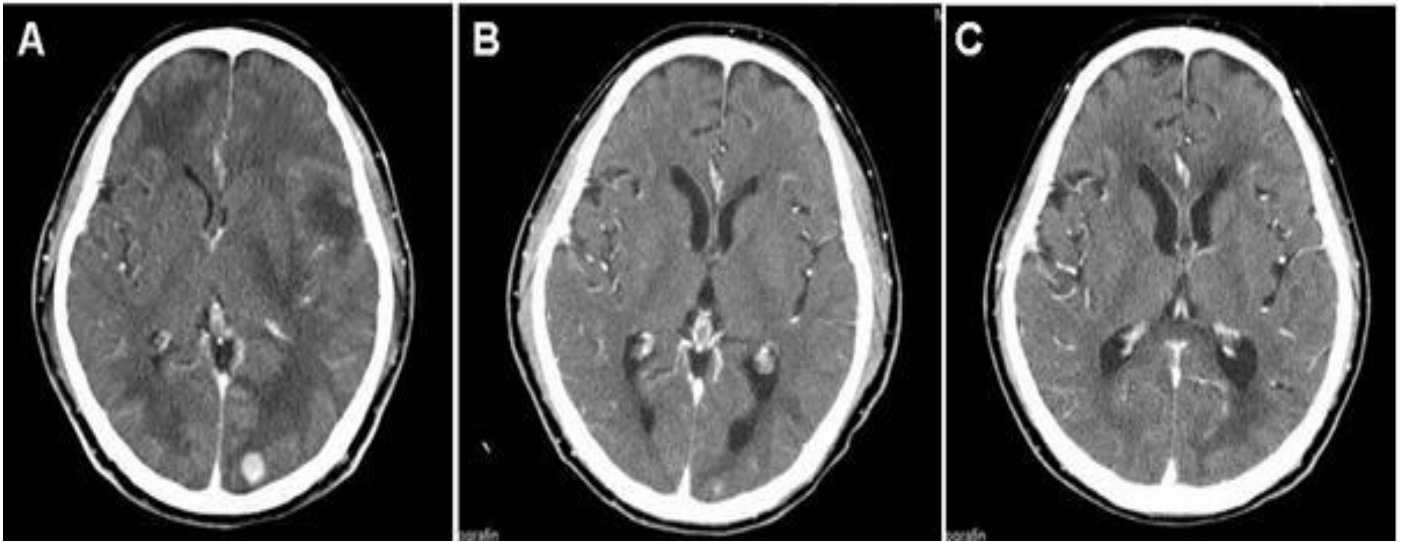


Figure 1. (A) The brain computerized tomography (CT) at presentation reveals cerebral tumors with multi-focal edema and ventricle compression. (B) Follow-up brain CT done after concurrent chemo-radiotherapy shows regressive change of the brain tumor. (C) During the recurrence of seizure just after erlotinib administration, brain CT does not show any sign of brain tumor progression.

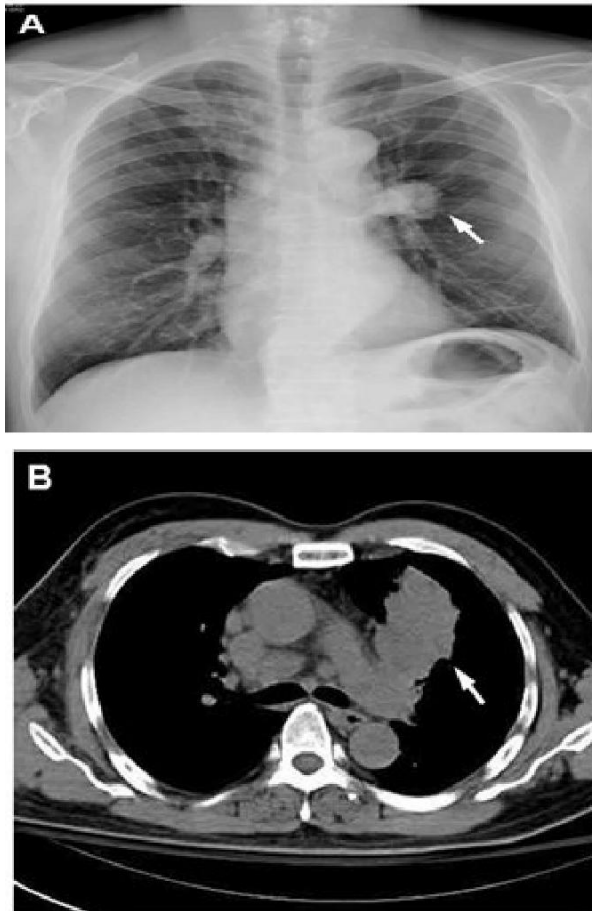


Figure 2. Chest X-ray (A) and CT (B) at initial presentation reveal left upper lobe pulmonary tumor (arrows) which was proved to be a pulmonary adenocarcinoma.

introduced after the diagnosis of lung cancer. Concurrent brain irradiation therapy was applied without any complication. During the 6-cycle chemotherapy and the maintenance treatment on phenytoin, patient was kept in stable disease status and did not encounter any seizure attack in that period. Follow-up brain CT also showed regressive change of the brain tumor (Figure 1B).

After completion of first-line chemotherapy, target therapy was introduced with the concern of tumor progression. The phenytoin therapy was continued as well with a good compliance. Unfortunately, just 5 days after the initiation of the treatment with erlotinib, generalized convulsion occurred and patient was sent back to hospital. The brain CT did not show any sign of brain tumor progression (Figure 1C). However, the serum phenytoin level was checked simultaneously and the level was as low as 1.65 ug/ml. Phenytoin was again loaded intravenously and maintenance dose was increased to 400 mg per day. The plasma phenytoin concentration check one month later was 7.72 ug/ml. The dose of phenytoin was not changed since seizure never happened thereafter.

Right subaxillary lymph nodes enlargement was observed after two months of erlotinib use. Under the impression of tumor relapse, erlotinib was replaced by pemetrexed which was another chemotherapeutic agent. The patient was then well controlled both in neurologic and pulmonary manifestations. The plasma phenytoin concentration was increased to 11.80 ug/ml two month after medication switch. During the treatment course, serum albumin levels checked periodically were all within normal range (3.2 to 3.9 g/dL) and there was no manifestation of hypoalbuminemia.

DISCUSSION

We report a NSCLC patient complicated with brain metastasis receiving phenytoin whose seizure recurred after the introduction of erlotinib. This suggests that erlotinib may enhance the metabolism of phenytoin and may result in low plasma phenytoin level.

Brain metastasis is a common manifestation in patients with advanced NSCLC. Some NSCLC patients were initially diagnosed in spite of the absence of pulmonary manifestation simply owing to the symptoms of central nervous system, such as headache, vertigo, hemiplegia, and convulsion. NSCLC-induced seizure usually requires anticonvulsants in addition to brain irradiation therapy. Concurrent chemotherapy is usually applied in order to prolong the survival in patients with good performance. Drug-drug interactions are possible during such treatment since both anticancer and antiepileptic medication may share the common metabolic pathways. Among the anticonvulsants, carbamazepine, phenytoin, phenobarbital, and primidone were found to have prominent cytochrome P450 (CYP) enzyme-induction effects, while valproic acid was shown to have an inhibitory effect (Yap et al., 2008). Induction or inhibition of CYP enzymes by anticonvulsant can cause a decrease or increase in anticancer drug concentrations. Similarly, enzyme inhibition or induction by anticancer drugs may also lead to anticonvulsant toxicity or loss of seizure control (Yap et al., 2008).

Target therapy agents inhibit EGFR in NSCLC cells and are usually favored due to relatively lower side effects and better responses in some patients, particularly in Asian population. Among the agents of target therapy, erlotinib is able to be administered orally and daily by which patient compliance can be improved. It may enhance CYP enzymes thus may have interaction with other drugs (Prod Info Tarceva (TM), 2004). Nevertheless, the drug-drug interaction between erlotinib and phenytoin had rarely been reported. It is possible that erlotinib use can enhance the metabolism of phenytoin and lower the serum phenytoin level by enhancing CYP enzymes. On the contrary, Grenader reported a case whose phenytoin level was elevated by erlotinib (Grenader et al., 2007).

The mechanism of phenytoin toxicity induced by erlotinib was not elucidated at that time. We report this case using both phenytoin and erlotinib with an opposite manifestation with Grenader's report. Since both drugs are CYP enzymes inducers, a decreased phenytoin level should be more common than an elevated phenytoin level while erlotinib is introduced. Thus, the case reported by Grenader needed further investigation to see if there was another factor inhibiting phenytoin metabolism. Although different results have been shown by Grenader and us, it is evident that drug interaction between erlotinib and phenytoin persists. It is possible that erlotinib can alter the phenytoin level in both directions. Periodical

serum phenytoin level check should therefore be warranted in such circumstance. In addition, it requires further investigation whether genetic factor such as gene polymorphism plays a role.

In the present report, we did not check the serum phenytoin level before the introduction of erlotinib. Therefore, the direct effect of erlotinib on phenytoin metabolism could not be clarified. However, the recurrence of seizure and low serum phenytoin level detected just after erlotinib use suggest a significant drug-drug interaction between these two drugs. In addition, the brain CT performed at the recurrence of seizure may help to exclude the possibility of brain tumor progression. Plasma phenytoin concentration increased significantly after the increment of phenytoin dosage, and it increased further after discontinuance of erlotinib. No more convulsions were observed ever since. In addition, although not closely monitored, the serum albumin levels checked periodically were within normal range and there was no manifestation of hypoalbuminemia such as edema. Therefore, the decreased phenytoin level was less likely resulted from low serum albumin level in this patient. Accordingly, it is highly possible that the introduction of erlotinib lowered the serum phenytoin level which induced the recurrence of seizure. Meanwhile, Chhun and colleagues showed that the administration of phenytoin decreased serum level of gefitinib, another target therapy agent commonly used in NSCLC (Chhun et al., 2009).

The effect of erlotinib might also be compromised by phenytoin (Prod Info Tarceva (TM), 2004). Accordingly, it is possible that there are significant drug interactions between both phenytoin and target therapy agents and the blood concentrations of both drugs could be lowered. It is also possible that such interactions are usually under-recognized due to limited clinical experience and the lack of routine application of drug monitoring. (Perucca, 2005). Therefore, whenever target therapy and antiepileptic agent (phenytoin in particular) are administered simultaneously, their drug levels should be monitored periodically.

In summary, we reported a case with advanced NSCLC associated with brain metastasis in which the use of erlotinib lowered plasma phenytoin level and induced recurrence of seizure. This suggested that erlotinib use may enhance the metabolism of phenytoin. Close attention on the drug interaction should be paid if both drugs are to be administered simultaneously.

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