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CASE REPORT

Favorable response to icotinib in a lung cancer patient with a special mutation at exon 19 of epidermal growth factor receptor

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Abstract

Many studies have illustrated that two types of mutation – deletions in exon 19 and a point mutation in exon 21 (L858R) – have been reported to comprise up to 90% of all activating epidermal growth factor receptor (EGFR) mutations. A point mutation at exon 19 is a rare mutation, and to date there have been no reports investigating the sensitivities of EGFR-tyrosine kinase inhibitors (TKIs) to the mutation. In this case report, we have demonstrated a special mutation, a point mutation at c.2279T>C (p.L760P) in exon 19 of EGFR, which has responded favorably to icotinib in a lung adenocarcinoma patient with brain metastasis. Icotinib is a new type of oral EGFR-TKI developed in China and is the first EGFR-TKI in Asia. Icotinib has the potential to improve the prognosis of lung adenocarcinoma patients and with less toxic-effect.

Case report

A 70-year-old man was admitted to the hospital with a cough and hemoptysis in November 2011. He was initially troubled with the cough and blood in the sputum, but didn't consult a doctor until the blood gradually increased and filled the sputum. He underwent a chest computed tomography (CT) scan at the outpatient department which showed a mass on the right lower lobe of the lung, enlargement of multiple lymph nodes at the mediastinum and right hilar, diffuse lymphatic miliary shadows in the right pulmonary, small nodes on the bilateral lobes, plural effusion on the right side and, at the same time, adenocarcinoma cells were found in the sputum. He had lost 10 kg over the past six months. He had also suffered from atrial fibrillation for more than 20 years. In his twenties, he had suffered from tuberculosis on his lungs. After being admitted, he completed the staging examinations. Abdominal magnetic resonance imaging (MRI) showed a liver cyst, angioma, cholecystolithiasis, and a kidney cyst, but there was no metastasis in the abdomen. A brain MRI scan showed a mass on the right cerebrum occipital lobe with circumambient dropsy. A bone scan showed adnominal intake in the No. 10 and 11 right articulations of the vertebrae. A diagnosis of Stage IV (cT4N3M1b) lung adenocarcinoma, atrial fibrillation, and obsolete pulmonary tuberculosis was made. The patient had primary focus in the right lower lobe of the lung and metastasis in the bilateral lobes of the lung, ipsilateral, mediastinal, and supraclavicular lymph nodes and brain. Biopsy and histologic examination of the lung mass in the right upper lobe were performed and showed adenocarcinoma. Immunohistochemistry (IHC) was positive for cytokeratin 7 (CK-7) and thyroid transcription factor-1 (TTF-1) and negative for CK 20. The patient rejected chemotherapy, preferring targeted therapy. Subsequently, we detected epidermal growth factor receptor (EGFR) and KRAS mutations by a direct sequencing test. These results revealed a special mutation at exon 19 of EGFR, which is a point mutation at c.2279T>C (p.L760P) (Fig 1), but no mutation on KRAS. There are no previous studies detailing the effect of EGFR- tyrosine kinase inhibitors (TKIs) on this mutation. Eventually, the patient decided to try to take icotinib 125 mg three times per day (TID) from 29 November 2011 as first-line therapy. The patient's cough and hemoptysis disappeared within 10 days of initiation. After discharge, he was checked again one, three, and five months after the initiation of icotinib (Fig 2). Both the primary and metastasized tumors, including the brain, showed significant shrinkage without any side effects, such as rash, diarrhea, and abnor

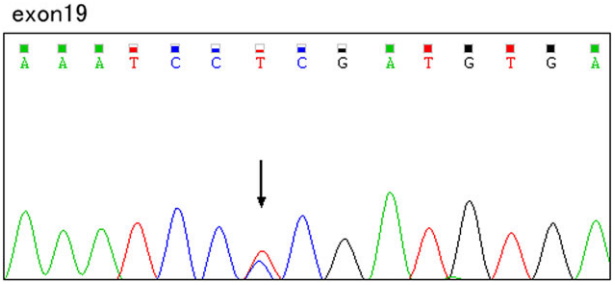

Figure 1 Exon 19 of gene epidermal growth factor receptor mutation plot. There is a point mutation at exon 19 located at c.2279, T changed by C. Subsequently, amino acid L changed by P is located at p. 760.

malities of transaminase. The patient received icotinib for 16 months in total and his progression-free survival (PFS) period was nine months. The patient continued medication for seven months after disease progression, and then discontinued until further significant progression. Chemotherapy was performed at this time. The patient is still alive and receiving follow-up.

Discussion

Icotinib is a new type of oral EGFR-TKI developed in China (Conmana, Zhejiang Beta Pharma, China) and is the first EGFR-TKI in Asia. A randomized, double-blind, multicenter, controlled, and head-to-head (icotinib vs. gefitinib) phase III trial of icotinib (ICOGEN)[1] has been conducted in China. ICOGEN is the first phase III study to prospectively compare

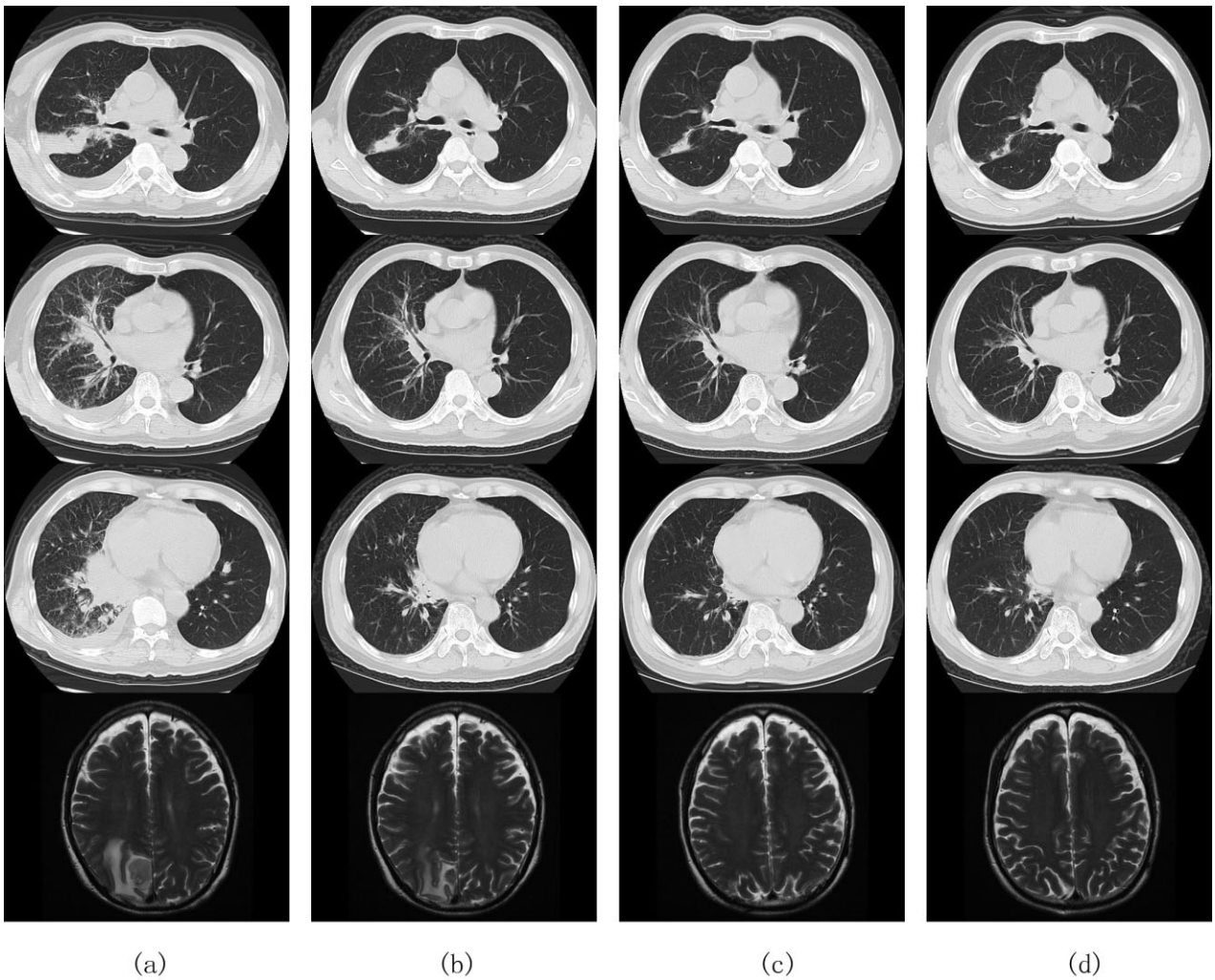

Figure 2 Chest computed tomography (CT) and brain magnetic resonance imaging (MRI) before and after treatment with icotinib. (a) Chest CT and brain MRI before icotinib treatment. (b) Chest CT and brain MRI one month after icotinib treatment. (c) Chest CT and brain MRI three months after icotinib treatment. (d) Chest CT and brain MRI five months after icotinib treatment.

two molecularly targeted agents head to head in pretreated NSCLC patients. The results demonstrated that icotinib is non-inferior to gefitinib in terms of PFS (4.6 months vs. 3.4 months, $P = 0.13$), overall survival (OS) (13.3 months vs. 13.9 months, $P = 0.88$), and tumor response rate (27.6% vs. 27.2%), but with less toxicity ($P = 0.05$) in NSCLC patients previously treated with one or two chemotherapy agents. Compared to other EGFR-TKIs, patients harboring active EGFR mutations have a better response to icotinib than those without EGFR mutations. Since August 2011, this drug has been available in the Chinese market. The recommended dose is 125 mg TID orally. In the present study, we report a case with lung adenocarcinoma harboring a special EGFR mutation at exon 19 which showed a favorable response to icotinib. This is an encouraging result, suggesting that icotinib may become an alternative for use in clinical settings.

Many studies have illustrated that mutations associated with sensitivity to EGFR-TKIs are found in exons 18–21 of the EGFR gene.[2,3] Two types of mutation – deletions in exon 19, clustered around the amino-acid residues 747–750, and a specific point mutation in exon 21 (L858R) – have been reported to comprise up to 90% of all activating EGFR mutations.[2–4] However, there are other rare mutations for which EGFR-TKI efficacy is unknown. In this case, the patient harbors a special mutation, a point mutation at exon 19 (c.2279T>C [p.L760P]). To date, there have been no studies detailing the activities of EGFR-TKIs on this type of mutation. In our case, the patient showed a very good response to icotinib, with a confirmed partial response (including the brain metastasis), improved performance status and long PFS. A change in the structure of the protein point mutation at exon 19 may have a response to icotinib similar to the deletions in exon 19.

Brain metastasis in NSCLC still is a challenge because of the poor prognosis. The treatment options for patients with brain metastasis include surgery, whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), or a combination of these. The survival time for patients receiving therapy is three to six months.[5] Chemotherapy has not been a standard treatment for these patients because drugs cannot effectively penetrate the blood–brain barrier. However, there have been several studies on the favorable efficacy of EGFR-TKIs on brain metastasis. Most of these reports are on gefitinib and erlotinib.[6–10] These EGFR-TKIs achieved a median OS of 8.3–18.8 months,[8,9,11,12] and both are known to cross the blood-brain barrier.[13,14] There have also been reports of high-dose EGFR-TKIs for brain metastasis.[15–18] However, there are few reports concerning the effects of icotinib. In our case, the patient had an asymptomatic brain metastasis on the right cerebrum occipital lobe with peritumoral edema. There has been significant remission to the lesion and after six months, it is almost undetectable. Surprisingly, though the lesion in the lung progressed, the brain metastasis remained stable. The significant relief in brain metastasis indicates that icotinib can cross the blood-brain barrier and can be used in regular doses (125 mg, TID) for NSCLC patients with brain metastasis. Previous studies have shown that the three EGFR-TKI molecules have similar structures and icotinib has the smallest molecular weight.[19–21]

EGFR-TKIs have similar toxic-effects, such as rash, diarrhea, liver dysfunction, and interstitial lung disease. However, because the recommended dose of erlotinib is closer to the maximum tolerated dose, it is moderately more toxic than gefitinib. The discontinuation of erlotinib and gefitinib because of toxic effects occurs in 5% and 2% of patients, respectively.[22,23] In the ICOGEN trial, the main toxic effects observed included rash and diarrhea, the same as other EGFR-TKIs. Most of the toxic effects were of grade I or II and were reversible. No patient required drug discontinuation because of toxic-effects. In our case, icotinib showed no toxicity and excellent tolerability. These results confirmed once again that icotinib is well tolerated.

Resistance to icotinib occurred after nine months, which matches the results of other EGFR-TKIs. After resistance, the disease progressed slowly at first, becoming more rapid, though the patient is still taking icotinib. As reported previously, continuation of treatment is needed even if the disease shows progression, as tumor growth would be accelerated to a greater degree if treatment were discontinued.[24] A limitation to this study is that the resistance pattern is not available, because re-pneumocentesis was not possible.

Conclusion

In summary, we have demonstrated that a rare mutation, a point mutation at exon 19 of EGFR, can respond favorably to icotinib. As a molecular targeted drug, icotinib may have the potential to improve the prognosis of NSCLC patients with less toxic-effects. Furthermore, we must investigate the mechanisms underlying the resistance of icotinib to develop new treatment strategies.

Disclosure

No authors report any conflict of interest.

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