CASE REPORT

Pharmacokinetic analysis of gefitinib in a patient with advanced non-small cell lung cancer undergoing hemodialysis

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Keywords
Gefitinib; lung cancer; renal failure.

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Received: 30 December 2014;
Accepted: 11 March 2015.
doi: 10.1111/1759-7714.12263

Thoracic Cancer 7 (2016) 251–253

Introduction

Although the discovery of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and the discovery of activating mutations of EGFR in a subset of patients with non-small cell lung cancer (NSCLC) introduced the era of personalized therapy in NSCLC beginning in 2004, the treatment experience for patients with NSCLC with chronic renal failure (CRF) undergoing hemodialysis (HD) has been less than ideal. More and more patients undergoing HD will be diagnosed with lung cancer because recent advances in HD have resulted in longer survival. However, patients undergoing HD are frequently elderly and have poor performance status (PS), and they usually cannot withstand chemotherapy because of its toxicities.

Gefitinib is an orally targeted EGFR-TKI that has demonstrated novel anti-tumor activity in patients with advanced NSCLC, even in those who had previously received chemotherapy. Therefore, patients who are unable or unwilling to endure the severe toxicity or inconvenience of chemotherapy may benefit from gefitinib administration. Because gefitinib is mainly metabolized by the liver and its excretion occurs mostly through bile excrement, it may be effective and safe in patients with CRF undergoing HD.1

Here, we report the case of an elderly woman undergoing HD who was diagnosed with advanced non-small cell lung cancer and treated with orally administered gefitinib. We analyzed the pharmacokinetic data of gefitinib in this patient and found that that gefitinib was safe under these conditions.

Case report

A 75-year-old female non-smoker who was diagnosed with lung adenocarcinoma and underwent lower right lobectomy (pT1N0M0, stage IA) 18 years prior to our report complained...
of an intermittent mild fever and cough for two months and was admitted to our hospital. She was affected by CRF as a result of hypertension and had undergone HD three times a week and hemofiltration twice a month for the past nine years. A computed tomography (CT) scan of the chest showed a mass in the upper lobe of the right lung near the mediastinum and multiple small nodules in the bilateral lung (Fig 1). Positron emission tomography (PET)-CT revealed that the mean standard uptake value of the mass was 4.5, the uptake of the multiple nodules elevated, and the abdominal uptake value was normal. Tumor relapse was confirmed based on these results. Because of her advanced age, poor PS, CRF requiring HD, and the toxicity of chemotherapy, chemotherapy was inappropriate for this patient. An EGFR DNA sequencing analysis was performed on her tumor tissue, which was obtained 18 years ago, revealing an L858R mutation in exon 21. The patient gave written informed consent and started oral gefitinib treatment at a dose of 250 mg daily. We then performed a PK analysis of gefitinib.

Seven days after the initiation of a daily 250 mg dose of gefitinib, we obtained blood samples in heparinized tubes at zero, two, four, six, and 10 hours after administration on the days in which the patient did not receive HD. Additional blood samples were drawn at 25 and 29 hours (the times before and after HD the next day). Plasma was isolated by centrifugation at 3000 × g at 4°C for 10 minutes within one hour of collection. The plasma was then transferred to screw-cap polypropylene tubes and frozen at −80°C until further analysis. The gefitinib concentration in the plasma samples was determined using validated high-performance liquid chromatography coupled with tandem mass spectrometry in the Clinical Pharmacology Research Center Laboratory of Peking Union Medical College Hospital (PUMCH), as previously reported.2

As shown in Figure 2, the peak plasma concentration of gefitinib occurred six hours after administration, with a peak of 456 ng/mL on non-HD days and 463 ng/mL on HD days. Twenty-four hours after administration, the plasma concentration of gefitinib decreased to 386 ng/mL. The plasma concentration of gefitinib was 376 ng/mL before HD and 463 ng/mL after HD. Two weeks after the initiation of daily 250 mg gefitinib administration, the patient received hemofiltration. We then performed a PK analysis of gefitinib before and after hemofiltration. The plasma concentration of gefitinib was 499 ng/mL before hemofiltration and 766 ng/mL after hemofiltration.

One month after the start of daily administration of 250 mg gefitinib, the patient’s symptoms improved and thoracic CT scans showed that the tumor had reduced in size. This evaluation demonstrated a partial response of her disease. Eight months later, the tumor increased in size and the patient died of metastasis of the tumor one year after treatment with gefitinib. No severe adverse effects were reported during gefitinib administration.

**Discussion**

Although there have been advances in the treatment of lung cancer, there is currently no standard therapy for patients with NSCLC and CRF. Almost all chemotherapy clinical trials in patients with lung cancer exclude patients with CRF. Some EGFR-TKIs, such as gefitinib and erlotinib, are mainly metabolized by the liver, and their excretion mostly occurs in bile excrement. Renal elimination of gefitinib and its metabolites accounts for less than 4%. In human plasma, over 90% of gefitinib combines with plasma proteins.1 However, there is little data available on the effectiveness and safety of EGFR-TKIs in patients with NSCLC and CRF who are undergoing...
HD. Togashi et al. analyzed the PK of erlotinib in three patients with NSCLC and CRF who were undergoing HD and five patients with NSCLC and normal organ function. Their results showed that erlotinib pharmacokinetics were only minimally affected by renal function and HD, and there were no serious adverse events in any cases. Rossi et al. reported that gefitinib was safe in two patients with NSCLC and renal failure. Shinagawa first analyzed the PK changes of gefitinib in patients with advanced NSCLC and CRF who were undergoing HD and showed that the PK pattern after gefitinib administration was similar to patients with normal renal function. This study found that 88.7% of gefitinib was retained in the plasma during HD.

As a previous study has reported, the plasma concentration of gefitinib four hours after administration in patients with normal renal function was determined to be approximately 298–872 ng/mL using the same analysis method used in the Clinical Pharmacology Research Center Laboratory of PUMCH. The peak plasma concentration of gefitinib in our patient was in the range observed in patients with normal renal function. The peak plasma concentrations of gefitinib on HD days were higher than the peak concentrations observed on days in which the patient did not receive HD. We consider that the increase in plasma gefitinib concentration after four hours of HD was a result of performing HD during the absorption phase of gefitinib.

Our results were not consistent with those of Shinagawa et al. who found that 88.7% of gefitinib was retained in the plasma during the course of HD. They concluded the influence of HD by calculating the gefitinib concentration before and after HD on the same day. In our opinion, the plasma concentration of gefitinib should decrease with time without HD; therefore, we concluded that HD or hemofiltration did not decrease the concentration of gefitinib. However, gefitinib concentration should be increased temporarily because of hemoconcentration after HD and hemofiltration. No severe toxicities were reported in this patient, and the treatment resulted in a partial response.

**Conclusion**

Gefitinib was determined to be safe in this patient with advanced NSCLC and CRF who was receiving HD. Although this is just one case, our findings suggest that gefitinib can be given to patients with NSCLC and CRF who are undergoing HD, and this treatment may result in improved survival for this population.

**Disclosure**

No authors report any conflict of interest.

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