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Case Report

Successful Treatment with Osimertinib Based on Therapeutic Drug Monitoring in a Hemodialysis Patient with Non-Small Cell Lung Cancer: A Case Report

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Epidermal growth factor receptor mutation · Osimertinib · Plasma concentration · Hemodialysis · Case report

Abstract
Although osimertinib is a key drug in the treatment of non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation, the safety in hemodialysis patients has not been established. A 76-year-old man was diagnosed with NSCLC with EGFR deletion mutation in exon 19. After treatment failure with first- and second-generation EGFR tyrosine kinase inhibitors, a T790M mutation was revealed by liquid biopsy. Hemodialysis was started three times a week because chronic renal failure worsened during treatment. Although the subsequent administration of osimertinib (80 mg daily) resulted in a tumor shrinkage and a gradual increase in the plasma concentration of osimertinib, which resulted in grade 3 general fatigue, reducing the dosage of osimertinib decreased its plasma concentration, leading to an improvement in his adverse event. Subsequently, with by adjusting the dosage while periodically measuring the

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plasma concentration of osimertinib, a stable therapeutic effect was sustained over the long term with no symptoms. Periodic plasma concentration measurements may be indispensable for successful treatment with osimertinib in hemodialysis patients.

Introduction

Globally, lung cancer is one of the most frequently diagnosed cancers and is the highest cause of cancer death [1]. Worldwide, the number of lung cancer deaths is expected to grow to three million by 2035 [2]. The epidermal growth factor receptor (EGFR) mutation is the most common mutation found in non-small cell lung cancer (NSCLC). In Asia, EGFR mutation is found in 51.4% of patients with NSCLC [3]. EGFR tyrosine kinase inhibitor is dramatically effective to NSCLC patients with EGFR mutation but is usually ineffective within a year due to acquired resistance such as T790M gene mutation. Recently, a cell-free DNA test isolated from plasma is used clinically to detect T790M gene mutation. This plasma test is less invasive than tissue biopsy and has been reported to be useful in overcoming the intratumor and inter-metastatic heterogeneity of tumor genetic profiles [4, 5]. In Japan, osimertinib, a third-generation EGFR tyrosine kinase inhibitor, was approved for the treatment of NSCLC with EGFR mutation after the acquisition of T790M-mediated resistance in 2016 and also approved as a first-line therapy for NSCLC with EGFR mutations in 2018. Its demand is increasing year by year.

The evidence of the anticancer drugs to hemodialysis patients is limited. Osimertinib is primarily metabolized by the liver and is eliminated in the feces (68%). The rate of osimertinib elimination in the urine is usually reported to be approximately 14% [6]. On the other hand, osimertinib is difficult to remove by hemodialysis because of its ease of combination with plasma proteins, small molecular weight, and large distribution volume [7]. There are some reports on the safety of short-term osimertinib for patients with renal failure undergoing hemodialysis [7–9]; however, few studies have investigated the safety of long-term use. We report the case of a patient with NSCLC with EGFR mutation who has been treated with osimertinib for more than a year with a stable therapeutic effect while measuring the plasma concentration of osimertinib during hemodialysis. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531840).

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The patient was a 78-year-old man with a 30-pack-year smoking history. Figure 1 shows the time course of serum concentration of creatinine and his treatment history. He underwent right lower lobe segmentectomy for NSCLC with EGFR mutation (deletion mutation in exon 19) at our department in 2017. Positron emission tomography performed 2 years after the operation showed the uptake of 18F-fluorodeoxyglucose into the right pleura, and it was diagnosed as pleural dissemination. Hemodialysis was started three times a week because chronic renal failure worsened during the administration of gefitinib (250 mg every other day). One and half years after the start of gefitinib, a growing nodule was found in the stump of the right lung resection by computed tomography (CT), and this nodule was judged to be resistant to gefitinib. Next, afatinib (20 mg daily) was administered, but it was judged that the

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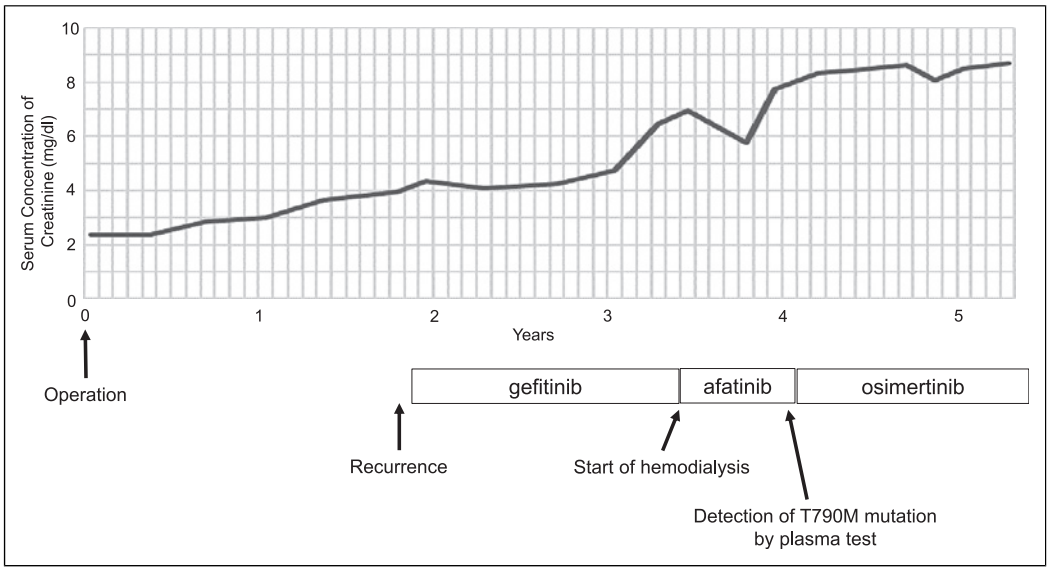

Fig. 1. Time course of serum concentration of creatinine and treatment history. The lung cancer recurred, and treatment with gefitinib was started about 2 years after operation. The disease progressed one and half years after the start of gefitinib. Therefore, treatment was switched to afatinib. Serum creatinine concentration gradually increased over the course of that time, and hemodialysis was started. The disease progressed 3 months after the start of afatinib. A plasma test detected the T790M mutation, so treatment was switched to osimertinib.

disease had progressed based on CT performed 3 months later. At this time, a plasma EGFR gene mutation test revealed a T790M point mutation, so the daily administration of osimertinib (80 mg [560 mg/week]) was started. He weighed 57.1 kg before starting osimertinib. He took osimertinib after HD on and at the same time as hemodialysis days on non-hemodialysis days. The plasma concentrations of osimertinib were measured at 1 day, 1 week, and 3 weeks after its initiation, and then every 4 weeks thereafter. Blood sampling for the measurement was performed before the administration of osimertinib on non-hemodialysis days. Hemodialysis was performed using a polysulfone membrane (MFX17M eco, Nipro, Osaka, Japan). The plasma concentrations of osimertinib were measured using a liquid chromatograph-tandem mass spectrometer (LC-MS/MS) system (AB SCIEX 3200 QTRAP LC-MS/MS; SCIEX, Tokyo, Japan, and LC-20; Shimadzu, Kyoto, Japan). Before osimertinib treatment, CT showed a 22-mm nodule in the right upper lobe (Fig. 2a). At 8 weeks after starting osimertinib, the lesions disappeared on CT (Fig. 2b), and no regrowth was observed after 15 months (Fig. 2c). However, the plasma concentration of osimertinib increased and reached 1,522.9 nM 20 weeks after the start of osimertinib. At that time, he was complaining of severe fatigue. At 8 weeks after the dosage of osimertinib was reduced to three times a week (240 mg/week), the plasma concentration decreased to 560.8 nM; thus, the dosage was increased to four times a week (320 mg/week). At this point, his complaints of fatigue had disappeared. However, plasma concentrations of osimertinib gradually decreased even after increasing dosage. Nine months after starting reduction of dosage, the plasma concentration decreased to 397.2 nM. The dosage was increased stepwise to 6 times a week (480 mg/week) because there was concern that the antitumor effect might be weakened due to a decrease in the plasma concentration (Fig. 3). The therapeutic effect was maintained for more than 1 year with no symptoms.

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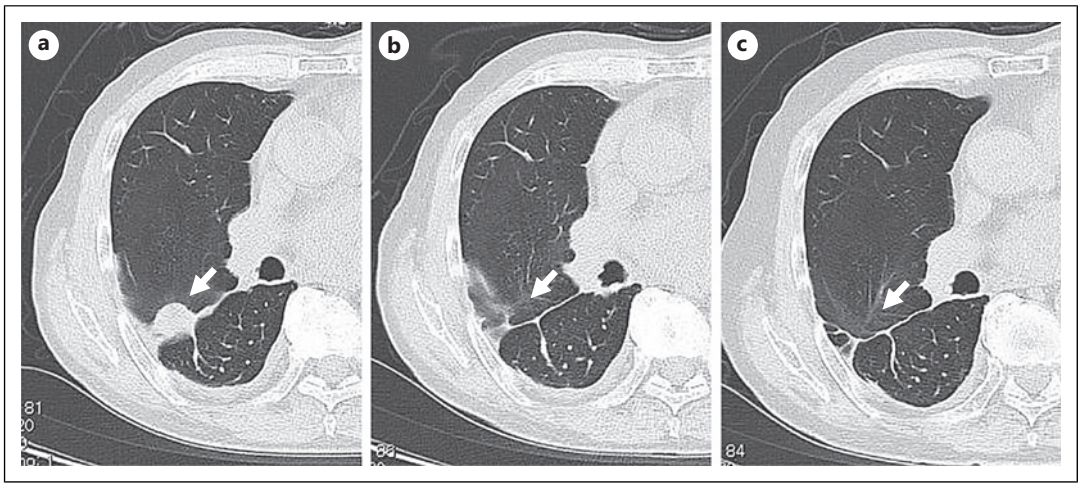

Fig. 2. Therapeutic effect of osimertinib by CT evaluation. Before osimertinib treatment, CT showed a 22-mm nodule in the right upper lobe (**a**). At 8 weeks after starting osimertinib, the lesions disappeared on CT (**b**), and no regrowth was observed after 15 months (**c**).

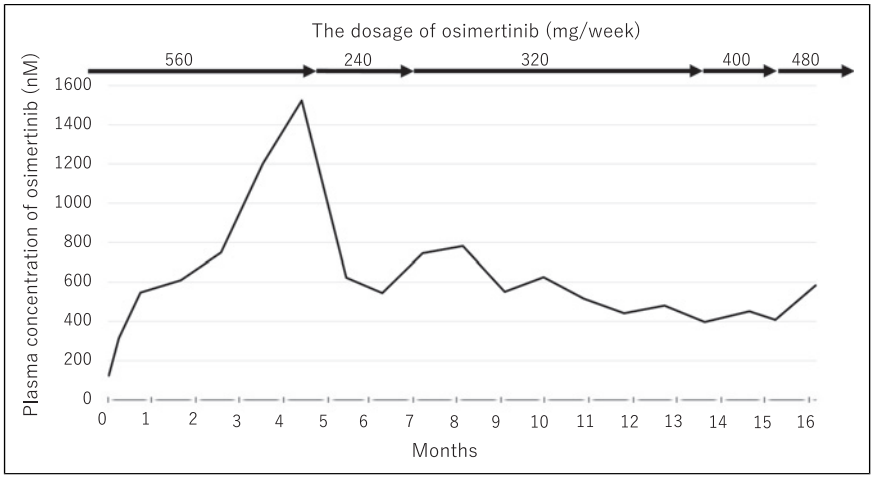

Fig. 3. Dosage of osimertinib and the course of its plasma concentration. The plasma concentration of osimertinib increased and reached 1,522.9 nM 20 weeks after the start of osimertinib. At 8 weeks after the dosage of osimertinib was reduced to three times a week (240 mg/week), the plasma concentration decreased to 560.8 nM; thus, the dosage was increased to four times a week (320 mg/week). However, plasma concentrations of osimertinib gradually decreased even after increasing dosage. Nine months after starting reduction of dosage, the plasma concentration decreased to 397.2 nM. The dosage was increased stepwise to 6 times a week (480 mg/week) with plasma concentration measurements.

Discussion

There is a dearth of data on the plasma concentration of osimertinib in patients undergoing hemodialysis. To our knowledge, there are three English-language case reports detailing the course of treatment with osimertinib to hemodialysis patients, and their observation periods ranged from 17 days to 9 months [7–9]. The observation period of this report, 16 months, is the longest in the relevant literature. Furthermore, this is the first study to report the results of long-term plasma osimertinib concentration measurement.

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In the AURA extension and AURA2 studies of NSCLC patients with a normal renal function, the mean Css max of osimertinib at a dose of 80 mg was 533–639 nM [10]. In study observing the pharmacokinetics of osimertinib, C_{max} and area under the concentration-time curve increased dose-proportionally over the range of 20 to 240 mg [11]. In another study based on predictive xenograft models, a starting osimertinib dose of 20 mg was chosen as sufficient to inhibit the T790M mutation, although doses equivalent to 80 mg or higher were expected to lead to stronger inhibition of tumor growth [12]. On the other hand, a clinical study involving a total of 780 patients found no relationship between osimertinib exposure and efficacy across 20 to 80 mg range [13]. Actually, the minimum plasma concentration that maintains the efficacy of osimertinib in human is unclear. A previous study showed that a higher plasma concentration of osimertinib increased the incidence and severity of adverse events [14]. Fujiwara et al. [15] reported that side effects with osimertinib occurred more frequently in patients with renal dysfunction and low body weight.

We introduced a normal dosage of osimertinib to an EGFR-mutated NSCLC patient with renal failure who was undergoing hemodialysis. The plasma concentration of osimertinib increased to a very high level of 1,522.9 nM at 20 weeks after the start of administration, and he complained of severe fatigue**.** It is suggested that the restricted elimination of osimertinib in the urine and the fact that osimertinib was not removed by hemodialysis were the reasons for the gradual increase in the plasma concentration of osimertinib. Decreasing dosage of osimertinib reduced its plasma concentration and improved his symptoms. After reducing the dosage of osimertinib, the plasma concentration continued to decrease gradually. So, the dosage of osimertinib was increased while monitoring the plasma concentration to ensure plasma concentration level comparable to those in patients with normal renal function. As a result, a stable tumor suppressive effect was obtained during the 16-month administration period of osimertinib. The relationship between long-term pharmacokinetics and efficacy of osimertinib in hemodialysis patients needs further investigation.

Limitation

Since it was limited to reporting on individual events, it is desirable to demonstrate it in clinical trials involving a larger number of patients in the future.

Conclusion

We considered that the periodic measurement of the plasma concentration of osimertinib should be performed to enable long-term treatment in patients with renal failure who are undergoing hemodialysis.

Statement of Ethics

The patient was fully informed and consented to the treatment he received. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. Ethical approval for osimertinib plasma concentration measurement was obtained from the Ethics Committee on Clinical Research, Sakuragaoka Campus, Kagoshima University (Approval number 170258).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.A., Y.T., T.S., and M.S. gave the initial idea. R.M., K.T., M.A., T.U., A.H.-T., and G.K. treated the patient. R.O. and H.T. measured plasma concentration of osimertinib. T.N. and K.U. recollected the data. K.T. and M.A. drafted the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data are included in this article. Further inquiries can be directed to the corresponding author.

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