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**Review EGFR-TKIs administration to non-small-cell lung cancer patients undergoing hemodialysis**

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**Abstract**

Non-small-cell lung cancer (NSCLC) causes significant mortality worldwide. Patients with chronic renal failure (CRF) have an increased risk of developing lung cancer. NSCLC Patients with CRF undergoing hemodialysis (HD) often exhibit poor performance and chemotherapy is generally contraindicated. Oral epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) are effective treatment agents for NSCLC patients. However, the benefits and adverse effects of EGFR-TKIs in NSCLC undergoing HD are known. There are no clinical studies on the effects of EGFR-TKIs on NSCLC patients undergoing HD. We reviewed all previous case reports about EGFR-TKIs in NSCLC patients undergoing HD. It is difficult to design studies about the effects of EGFR-TKIs in patients undergoing HD. This review is quite important. EGFR-TKIs are well tolerated in patients undergoing HD. The main routes of elimination of EGFR-TKIs are metabolism *via* the liver and renal elimination is minor. The recommended doses and pharmacokinetics of these EGFR-TKIs for patients undergoing HD are similar to those for patients with normal renal function. The plasma protein binding of EGFR-TKIs is very high and it is not necessary to adjust the dose after HD. In conclusions, EGFR-TKIs are effective and well tolerated in patients undergoing HD.

## INTRODUCTION

### **Impact of lung cancers**

Lung cancer causes significant mortality worldwide<sup>[1]</sup>. Lung cancer is classified into small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), with NSCLC accounting for 80–85% of lung cancer cases and adenocarcinoma accounting for 80% of NSCLC cases<sup>[1]</sup>. Despite the development of modern medicines, the outcomes of lung cancer remain poor<sup>[1]</sup>. The treatment of NSCLC depends strictly on the disease stage, and 80% of NSCLC patients are diagnosed at advanced (IIIb/IV) stages<sup>[1]</sup>. Since the lungs are often diagnosed at advanced stages and are unresectable, targeted therapy and chemotherapy are the major treatments for these patients<sup>[1]</sup>.

In general, chronic renal failure (CRF) patients undergoing hemodialysis (HD) exhibit a higher incidence of cancers, including lung cancer<sup>[2]</sup>. The risk factors for developing cancers include smoking, air pollution, genetic susceptibility, and occupational exposure<sup>[1]</sup>. It is suspected that the reasons for the higher incidence of cancers in patients undergoing HD are further related to weakened immunity, chronic inflammation, malnutrition, and impaired DNA repair<sup>[2]</sup>. CRF increases the incidence of cancers, as well as the difficulty in treating it. Therefore, the treatment of cancers in such patients is important.

For patients with cancer and CRF, who often exhibit poor performance, chemotherapy is generally contraindicated owing to its greater adverse effects (AEs). Moreover, chemotherapeutic drugs, such as cisplatin, are regarded as nephrotoxic agents and are not suitable for the treatment of CRF patients. Cisplatin is one of the most widely used chemotherapeutic agent for cancers. However, its clinical application is limited by its adverse effects, such as bone marrow suppression leading to hematopoietic abnormalities<sup>[3]</sup>. An increased incidence of adverse reactions to cisplatin has been reported in patients with renal insufficiency<sup>[4]</sup>. Therefore, the management of anti-cancer treatments for CRF patients undergoing HD is challenging.

Oral epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) are the promising treatment agents for NSCLC patients. EGFR is a transmembrane receptor

on the surface of epithelial cells and is considered an important molecular target in cancer treatment. EGFR gene mutation is a predictor of EGFR-TKI efficacy. EGFR-gene-activating mutations occur in 50–60% of Asian and 10–20% of Caucasian subjects with NSCLC<sup>[5]</sup>. Common mutations, including deletions in exon 19 and substitution of L858R in exon 21, comprise approximately 85% of EGFR mutations<sup>[5]</sup>. Rare mutations (about 15%) include point mutations, insertions, and deletions within exons 18–25 of the EGFR gene <sup>[5]</sup>.

EGFR-TKIs exert low side effects and less impact on kidney function, and patients exhibit better tolerability for them<sup>[6]</sup>. <sup>5</sup> EGFR-TKIs, including gefitinib and erlotinib (first-generation), afatinib (second-generation), and osimertinib (third-generation), <sup>7</sup> have shown significant benefits, with improved overall response rates (ORRs), longer progression-free survival (PFS), and better overall survival rate (OS) in patients with NSCLC harboring EGFR mutations<sup>[6]</sup>. Lung cancer patients undergoing HD sometimes exhibit poor performance; EGFR-TKIs are often a treatment choice for such patients. Since physicians worry about AEs and nephrotoxicity of chemotherapy agents in patients undergoing HD, EGFR-TKIs are often an optional strategy for such patients. However, most clinical trials have excluded patients undergoing HD, and the applicability of EGFR-TKIs for such patients <sup>11</sup> has not been studied. Therefore, we aimed to review the benefits, AEs, and pharmacokinetics of EGFR-TKIs in patients undergoing HD.

## Gefitinib

### Clinical benefits of gefitinib

Gefitinib was approved for metastatic NSCLC patients with sensitive EGFR mutations in July 2015<sup>[7]</sup>. <sup>8</sup> It has been demonstrated that using gefitinib as the first line of treatment for NSCLC with sensitive EGFR mutations results in an ORR of 62–71%, PFS of 8–13 months, and OS of 21–30 months <sup>[7]</sup>. The common AEs are skin rash, acne, and diarrhea <sup>[7]</sup>. Most AEs resolve on their own or after medical treatment. Elevation in liver function test parameters has been observed, but these elevations are often not

accompanied by any symptoms. The incidence of rare AEs, such as interstitial lung disease (ILD), is approximately 1%<sup>[7]</sup>.

#### **Clinical benefits of gefitinib in patients undergoing HD**

Bersanelli *et al* reported a 60-year-old female Caucasian non-smoker undergoing HD with right lung adenocarcinoma with mediastinal lymph nodes and bone metastasis<sup>[8]</sup>. Her initial ECOG PS score was 0, and she received radiation therapy on the spine and was administered gemcitabine and cisplatin. Owing to progression of bone metastasis after three cycles of gemcitabine and cisplatin, second-line treatment with gefitinib was initiated. Gefitinib induced a good response of the disease to treatment for 7 years without complications. Del Conte *et al* reported a 70-year-old male non-smoker undergoing HD with right middle lobe (RML) lung adenocarcinoma<sup>[9]</sup>. The patient underwent RML lobectomy for pT1N0M0 NSCLC (stage IA). After 3.5 years from surgery, recurrent lung adenocarcinoma with deletion of 15 nucleotides of exon 19 was found. He received gefitinib, and exhibited only a grade 1 cutaneous rash. After 2 years of gefitinib treatment, he was still in complete remission without serious AEs<sup>[9]</sup>. Bersanelli *et al* and Del Conte *et al* showed that gefitinib was effective and well tolerated in patients undergoing HD<sup>[8, 9]</sup>.

#### **Pharmacokinetics of gefitinib in patients with normal renal function (NRF)**

Most gefitinib is metabolized by the liver and excreted *via* feces (86%), and a small portion (7%) is excreted *via* urine (Figure 1A)<sup>[10]</sup>. Approximately 90% of gefitinib binds to plasma proteins in the blood<sup>[10]</sup>. The half-life of gefitinib is 41 h, and steady-state plasma concentrations are attained by day 7–10<sup>[11]</sup>. The maximum concentration ( $C_{max}$ ) is attained 5 h (3–7 h) after oral dosing, the median  $C_{max}$  is 377 (168–781) ng/mL, the area under the curve of the plasma concentration from 0 to 24 h ( $AUC_{0-24}$ ) is 4893 (698–13991) ng•hr/mL, and the trough concentration ( $C_{trough}$ ) is 410 (115–1021) ng/mL<sup>[11]</sup>.

#### **Pharmacokinetics of gefitinib in patients undergoing HD**

There are only two case reports on the pharmacokinetics of gefitinib in patients undergoing HD. Shinagawa *et al* performed the first pharmacokinetic analysis of gefitinib in a 58-year-old female non-smoker undergoing HD for 8 years<sup>[12]</sup>. She



developed lung adenocarcinoma (pT1N0M0, stage IA) and underwent left lower lobectomy (LLL)<sup>[12]</sup>. Two years later, she had recurrent lung cancer, which had metastasized to the left subclavian lymph node, and meningitis. The EGFR mutation showed a deletion of 15 nucleotides in exon 19 in tumor tissues. She was administered 250 mg gefitinib daily. The  $C_{max}$  and  $C_{trough}$  of gefitinib were 410.4 and 102.7 ng/mL, respectively. The plasma concentrations were 308.3 and 272.2 ng/mL before and after HD (88% maintained throughout HD), respectively<sup>[12]</sup>. There were no serious AEs following gefitinib administration<sup>[12]</sup>. Luo *et al* reported a 75-year-old female non-smoker with lung adenocarcinoma (pT1N0M0, stage IA) who underwent right lower lobectomy (RLL)<sup>[13]</sup>. Nine years later, she underwent HD due to hypertension. However, the lung cancer relapsed with multiple nodules in both lungs. EGFR mutations in the tumor tissue revealed an L858R mutation in exon 21. She was then administered 250 mg gefitinib daily. The  $C_{max}$  was 456 and 463 ng/mL on non-HD and HD days, respectively. The  $C_{trough}$  was 386 ng/mL. The plasma concentrations were 376 and 463 ng/mL before and after HD, respectively. The initial response to gefitinib was a decrease in tumor size, but the tumor increased in size after 8 mo of treatment. No severe AEs were reported after gefitinib administration.

The data on the pharmacokinetics of gefitinib in patients undergoing HD and NRF are shown in Figure 2. These data revealed that the pharmacokinetics of gefitinib in patients undergoing HD were similar to subjects with NRF<sup>[12, 13]</sup>. Since 90% of gefitinib is bound to plasma proteins<sup>[10]</sup>, it was rational that 90% of gefitinib was retained in the blood after HD. In addition, these patients showed a good response to gefitinib and did not have elevated AEs<sup>[12, 13]</sup>.

## Erlotinib

### Clinical benefits of erlotinib

Erlotinib is a reversible EGFR-TKI that was approved in 2004 for patients harboring EGFR exon 21 L858R mutations and exon 19 deletion<sup>[6]</sup>. Previous studies using erlotinib as the first line of treatment for NSCLC with sensitive EGFR gene mutations showed an

ORR of 58–83%, PFS of 9.7–13 months, and OS of 23–33 months<sup>[14]</sup>. Common AEs included skin rash, diarrhea, nausea, anorexia, dermatitis acneiform, fatigue, anemia, and ILD<sup>[14]</sup>. However, grade 3 or 4 AEs rarely occurred in subjects upon administration of erlotinib<sup>[6]</sup>.

#### **Pharmacokinetics of erlotinib in patients with NRF**

Most erlotinib is metabolized by the liver and excreted *via* feces (80–90%), and a small portion (9%) is excreted *via* urine (Figure 1B)<sup>[15]</sup>. Approximately 95% of erlotinib is bound to plasma proteins<sup>[15]</sup>. The half-life of erlotinib is  $21.86 \pm 28.35$  h and steady-state concentrations in plasma are attained by day 8–10<sup>[16]</sup>. The  $C_{\max}$  is attained  $3.69 \pm 3.21$  h after dosing, and the median  $C_{\max}$  is  $2290 \pm 840$  ng/mL. The median  $AUC_{0-24}$  is  $35760 \pm 15720$  ng•hr/mL<sup>[16]</sup>.

#### **Pharmacokinetics of erlotinib in patients undergoing HD**

Togashi *et al* reported three NSCLC patients undergoing HD who were treated with erlotinib<sup>[17]</sup>. Case 1 was a 74-year-old male ex-smoker undergoing HD for 5 years, who had lung adenocarcinoma (cT1N3M1, stage IV) without any EGFR mutations. Case 2 was a 74-year-old female non-smoker undergoing HD for 3 years, who had adenocarcinoma (cT2N0M0, stage IB) without any EGFR mutations. Initially, she received irradiation therapy with a dose of 54 Gy for the tumor. The tumor enlarged, with invasion to the chest wall, and metastasized to the hilar lymph node (cT3N1M0, IIIA). Case 3 was a 69-year-old male current smoker undergoing HD for 1 year, with lung squamous cell carcinoma (cT2N1M1, stage IV). All three patients were administered 150 mg erlotinib daily. Pharmacokinetic analyses of erlotinib were conducted on the first day (non-HD), eighth day (non-HD), and ninth day (HD)) after administration<sup>[17]</sup>. For these three patients undergoing HD, the  $C_{\max}$ ,  $C_{\text{trough}}$ , and  $AUC_{0-24}$  on day 1 were  $960 \pm 287$  ng/mL,  $338 \pm 116$  ng/mL, and  $13944 \pm 4590$  ng•hr/mL, respectively. On day 8 without HD, the  $C_{\max}$ ,  $C_{\text{trough}}$ , and  $AUC_{0-24}$  were  $1638 \pm 206$  ng/mL,  $494 \pm 336$  ng/mL, and  $23285 \pm 5338$  ng•hr/mL, respectively. On day 9 (HD day), the  $C_{\max}$  was  $1633 \pm 338$  ng/mL. The plasma concentrations of erlotinib before and after HD were  $1465 \pm 350$  and  $1360 \pm 375$  ng/mL, respectively. The pharmacokinetic parameters

on the ninth day were similar to those on the eighth day, indicating that erlotinib was hardly eliminated by HD. In addition, the data of patients undergoing HD were similar to subjects with NRF. There were no serious AEs in these cases.

The data on the pharmacokinetics of erlotinib in patients undergoing HD and subjects with NRF are shown in Figure 3. These data suggested that the pharmacokinetics of erlotinib in patients undergoing HD were similar to subjects with NRF<sup>[16, 17]</sup>. Since 95% of erlotinib is bound to plasma proteins <sup>[15]</sup>, it was rational that most erlotinib was retained in the plasma after HD.

## **Afatinib**

### **Clinical benefits of afatinib**

Afatinib is an irreversible covalent inhibitor of the ErbB receptor family, including EGFR, ErbB2/HER2, and ErbB4/HER4 <sup>[18]</sup>. It was approved by the FDA in 2013 for NSCLC with exon 21 L858R substitutions and exon 19 deletions <sup>[18]</sup>. Recent studies suggested that afatinib is effective against other uncommon mutations, such as L861Q in exon 21 and G719X in exon 18, and it was therefore approved by the FDA in 2018 for these uncommon EGFR mutations <sup>[18]</sup>. Previous studies using afatinib <sup>2</sup> as the first line of treatment for NSCLC with sensitive EGFR gene mutations showed an ORR of 70–81.8%, PFS of 13.4–15.2 mo, and OS of 27.9–49 mo <sup>[18]</sup>. The commonly reported AEs were diarrhea, skin rash, paronychia, mucosal inflammation, dry skin, stomatitis, skin fissures, nausea, dermatitis acneiform, and conjunctivitis <sup>[18]</sup>. Most AEs were of grade 1–2, and serious AEs were uncommon. However, serious AEs are more frequently reported for afatinib than for gefitinib and erlotinib<sup>[18]</sup>.

### **Pharmacokinetics of afatinib in patients with NRF**

Most afatinib is excreted through feces (85%), and a small amount (15%) is excreted *via* urine (Figure 1C) <sup>[19]</sup>. Approximately 95% of afatinib is bound to plasma proteins<sup>[20]</sup>. The half-life periods for 30 and 40 mg afatinib are 21.3 and 26.9 h, respectively<sup>[19]</sup>. Steady-state plasma concentrations are attained in approximately 8 days <sup>[19]</sup>. The C<sub>max</sub> is attained approximately 2–5 h after administration <sup>[20]</sup>. For daily administration of 30 mg



afatinib, the median  $C_{max}$ ,  $C_{trough}$ , and  $AUC_{0-24}$  are 16.3 ng/mL, 15.1 ng/mL (8.1–38.1 ng/mL), and 189 ng•hr/mL, respectively<sup>[21, 22]</sup>. For daily administration of 40 mg afatinib, the median  $C_{max}$ ,  $C_{trough}$ , and  $AUC_{0-24}$  are 25.2 ng/mL, 18.2–34.1 ng/mL, and 324 ng•hr/mL, respectively<sup>[21, 22]</sup>.

### **Clinical benefits of afatinib in patients undergoing HD**

Yamaguchi *et al* reported a 59-year-old male ex-smoker undergoing HD for 17 years<sup>[23]</sup> and diagnosed with stage IV lung adenocarcinoma (cT4N3M1b) with multiple pulmonary, hepatic, and bony metastases. Analysis of EGFR mutations revealed a G719A point mutation in exon 18. The patient received oral afatinib (30 mg) daily. The treatment was well tolerated, with only mild skin rash and no diarrhea. The tumors shrank after 2 mo of treatment. Bersanelli *et al* reported afatinib as a third-line treatment for an NSCLC patient undergoing HD<sup>[8]</sup>. Initially, the patient received cisplatin and gemcitabine (first-line) and gefitinib (second-line). After tumor progression, the patient was started on 30 mg afatinib daily. The treatment was well tolerated, with only mild asthenia. After 2 mo, the afatinib dosage was increased to 40 mg daily, which caused significant asthenia, vomiting, and nausea<sup>[8]</sup>.

The USA prescribing information recommends that the dose of afatinib be decreased to 30 mg daily for subjects with renal impairment. However, this recommendation cannot be made for patients with severe renal impairment or those undergoing HD, as afatinib has not been studied in these populations<sup>[20]</sup>. Based on these two case reports, we suggest that 30 mg afatinib is safe and effective in patients undergoing HD<sup>[8, 23]</sup>.

### **Pharmacokinetics of afatinib in patients undergoing HD**

Yamaguchi *et al* performed the first pharmacokinetic analysis of daily administration of 30 mg afatinib to patients undergoing HD<sup>[23]</sup>. The  $C_{trough}$  values were 10.2 (day 2), 15.7 (day 3), 22.8 (day 10), 27.3 (day 11), and 23.8 ng/mL (day 12). Steady-state concentrations were attained by day 12. Yamaguchi *et al* suggested that daily administration of 30 mg afatinib was safe for patients undergoing HD<sup>[23]</sup>. Imai *et al* also performed pharmacokinetic analysis of daily administration of 30 mg afatinib as first-

line afatinib therapy for three lung cancer patients undergoing HD <sup>[24]</sup>. Case 1 was a 78-year-old male with stage IV adenocarcinoma (cT1bN0M1b) with an EGFR mutation (exon 19 deletion). Case 2 was a 75-year-old male ex-smoker with lung adenocarcinoma (pT1aN0M0) with an EGFR mutation (exon 19 deletion) undergoing HD. However, postoperative mediastinal lymph nodes recurred. Case 3 was a 62-year-old male non-smoker with adenocarcinoma (pT2aN1M0) with <sup>12</sup> an EGFR mutation (exon 21 L858R). Multiple pulmonary metastases with malignant pleural effusion occurred after the surgery. The pharmacokinetic analyses of the three cases revealed that the  $C_{max}$  was  $13.4 \pm 6.2$  and  $51.7 \pm 23.8$  ng/mL on days 1 and 10, respectively, and the  $C_{trough}$  was  $4.5 \pm 2.3$  and  $28.3 \pm 9.0$  ng/mL on days 2 and 11, respectively. The principal AEs were skin rash, dry skin, diarrhea, and malaise, and no severe AEs were reported except one case of grade 3 diarrhea. All the patients were maintained at partial response until the article was published (135–456 days).

The data on the pharmacokinetics of afatinib in patients undergoing HD and subjects with NRF are shown in Figure 4. Since approximately 95% of afatinib is bound to plasma proteins<sup>[25]</sup>, afatinib is poorly eliminated during HD. The pharmacokinetics of afatinib in the aforementioned patients undergoing HD were comparable with subjects with NRF<sup>[25]</sup>.

## Osimertinib

### Clinical benefits of osimertinib

Osimertinib selectively and potently inhibits sensitive EGFR gene mutations <sup>[26]</sup>. Osimertinib also has a good response in NSCLC with acquired EGFR T790M resistance after treatment with first-or second-generation EGFR-TKIs.

Therefore, <sup>1</sup> it is an effective first-line treatment for NSCLC patients with activating EGFR mutations, and an effective second-line treatment for NSCLC patients with T790M resistance mutations <sup>2</sup> <sup>[26]</sup>. Previous studies using osimertinib as the first line of treatment for NSCLC with sensitive EGFR gene mutations showed an ORR of approximately 80%, PFS of 18.9 mo, and OS of 38.6 mo <sup>[26]</sup>. After administration of

osimertinib as the second-line treatment for NSCLC patients with T790 M resistance mutations, the ORR was approximately 71%, PFS was approximately 10.1 mo, and OS was 26.8 mo<sup>[27]</sup>. The common AEs of osimertinib were skin rash and diarrhea, and the others were paronychia, dry skin, stomatitis, nausea, anorexia, headache, constipation, anemia, pruritus, fatigue, and cough <sup>[27]</sup>. Osimertinib has fewer serious AEs than the first- and second-generation TKIs <sup>[27]</sup>.

### **Clinical benefits of osimertinib in patients undergoing HD**

Iwafuchi *et al* reported a 64-year-old female non-smoker undergoing HD with left lung adenocarcinoma (cT3N1M1a, stage IV, with malignant pleural effusion) with EGFR deletion in exon 19 <sup>[28]</sup>. She received gefitinib (first-line), erlotinib (second-line), taxotere (third-line), afatinib (fourth-line), and another six cycles of taxotere (fifth-line). After five years of treatment, the tumor was enlarged with liver and splenic metastases. For T790 M mutation, daily oral administration of 80 mg osimertinib was prescribed. The tumor improved to partial remission, and the liver and splenic metastases disappeared. The patient experienced no serious AEs and showed a good response. This case presented good effects and tolerability in patients undergoing HD even with sixth-line therapy.

### **Pharmacokinetics of osimertinib in patients with NRF**

Most osimertinib is metabolized by the liver and excreted *via* feces (68%), and a small portion (14%) is excreted *via* urine (Figure 1D) <sup>[29]</sup>. The plasma protein binding ability of osimertinib is very high (98%) <sup>[30]</sup>. The half-life is 48.3 h, and steady state plasma concentrations are attained in approximately 10 days <sup>[30]</sup>. The time to attain  $C_{max}$  is 6 h (3–24 h) after dosing; the  $C_{max}$  and  $C_{trough}$  are 371 and 230 ng/mL, respectively<sup>[31]</sup>.

### **Pharmacokinetics of osimertinib in patients undergoing HD**

Tamura *et al* reported the first pharmacokinetic analysis of osimertinib in patients undergoing HD <sup>[32]</sup>. They reported a 72-year-old male ex-smoker with lung adenocarcinoma (T2aN3M1b, stage IV, with pleural and bone metastasis) with EGFR exon 19 deletion. He was initially receiving 250 mg gefitinib daily, but the treatment was

discontinued, owing to liver toxicity, in 2 mo. After his recovery, he received 150 mg erlotinib daily and showed a good response. However, due to skin toxicity, the erlotinib dosage was gradually reduced to 50 mg daily. During the treatment, HD was initiated owing to worsening diabetic nephropathy. Four years after erlotinib treatment, the primary tumor was enlarged and had metastasized to the supraclavicular lymph nodes. The tumor tissue presented a T790M mutation in exon 20. He was initially administered 40 mg osimertinib daily for the previous liver and skin AEs of gefitinib and erlotinib. As treatment was well tolerated, pharmacokinetic analysis of osimertinib was performed 4 mo after administration<sup>[32]</sup>. Pharmacokinetic analysis of osimertinib (40 mg daily) was performed on HD and non-HD days. The  $C_{max}$  was 218 and 217 ng/mL on HD and non-HD days, respectively. The osimertinib dosage was increased to 80 mg daily for only mild AEs. Pharmacokinetic analysis was performed after 6 days and revealed that the  $C_{max}$  was 388 and 473 ng/mL on HD and non-HD days, respectively. The patient received 80 mg osimertinib daily, without any AEs <sup>[32]</sup>. Matsunashi *et al* reported a 66-year-old male undergoing HD with relapsed stage IV NSCLC with an EGFR mutation in exon 21 (L858R) 2 years after body radiotherapy <sup>[29]</sup>. He received 80 mg osimertinib daily as first-line treatment. The  $C_{max}$  was 400–476 and 335–351 ng/mL before and after HD, respectively. When osimertinib was administered on HD days, the  $C_{max}$  was 430 ng/mL <sup>[29]</sup>. The  $AUC_{0-24}$  before HD, after HD and on non-HD day were 7022–8842, 6376–7039 and 8631 ng•hr/mL.

The data on the pharmacokinetics of gefitinib in patients undergoing HD and subjects with NRF are shown in Figure 5. Since the protein binding ability of osimertinib is very high, its dialyzability rate is relatively low and it is minimally affected by HD <sup>[30]</sup>. The pharmacokinetic parameters on non-HD days were almost the same as those on HD days.

### Limitations of this review

This review has several limitations. Firstly, the literature cited in this review on EGFR-TKIs in patients undergoing HD are all case reports. There have been no cohorts or randomized controlled trials (RCTs) with EGFR-TKIs in patients undergoing HD.

However, it is difficult to conduct research on HD patients owing to their rarity. Therefore, this review is very important for providing recommendations for EGFR-TKIs in such patients. Secondly, this review focuses on EGFR-TKIs in lung cancer patients undergoing HD. It is unknown whether the conclusions drawn are applicable to other cancers.

## **CONCLUSION**

There have been no clinical studies on EGFR-TKIs in NSCLC patients undergoing HD. We suggest that EGFR-TKIs are suitable for such patients. The recommended doses and pharmacokinetics of these EGFR-TKIs for patients undergoing HD are similar to those for patients with NRF. EGFR-TKI treatment is effective and well tolerated in patients undergoing HD.



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