Abemaciclib in Patients with End-Stage Renal Disease and Advanced Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer: A Report of 2 Cases

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Keywords
Metastatic breast cancer · Estrogen receptor · Abemaciclib · End-stage renal disease

Abstract
Cyclin4/6-dependent kinase inhibitors (CDKIs) plus hormonotherapy currently represent the standard golden treatment for patients with estrogen receptor-positive (ER+), human epidermal growth factor receptor-2-negative (her-2−) advanced breast carcinoma. Among CDKIs, abemaciclib is the most active. No data on the use of abemaciclib in patients with end-stage renal disease (ESRD) exist in the medical literature. Two women with ER+, her-2− metastatic breast cancer received standard hormonal therapy plus abemaciclib 100 mg b.i.d. under strict monitoring for toxicity. Although ESRD exposes patients to a higher risk of toxicity from antineoplastic agents, no unexpected or severe toxicity was recorded in both patients after 9 and 12 months of therapy. In 1 patient, grade 2 diarrhea started after 7 days of therapy and disappeared or was significantly reduced after using loperamide and dietary modifications. Both patients complained of grade 1 asthenia. Hematological parameters were in line with expected toxicity. No cardiovascular or hepatic side effects were observed. This report of two women with metastatic breast cancer suggests the potentially safe use of abemaciclib in ESRD, which should be confirmed in more extensive real-life studies.
**Introduction**

The occurrence of end-stage renal disease (ESRD) increases mortality and morbidity of cancer patients through an increased risk of associated cardiovascular disease, diabetes, and hypertension [1]. Furthermore, even if best treated according to guidelines, women with breast cancer and ESRD display an increased risk of breast cancer mortality [2, 3]. This negative relationship is related to a complex interplay between pharmacological issues, comorbid illnesses, the inflammatory state with activation of cancer growth-promoting biomolecular pathways, cytokine release alterations, and immunologic response impairment [4, 5]. To date, the latest updated treatment guidelines of the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology report a combination of anti-hormonal agents and cyclin6/dependent kinase inhibitors (CDKIs) as the standard golden therapy for patients with estrogen receptor-positive (ER+), human epidermal growth factor receptor-2-negative (her-2−) advanced breast carcinoma [6, 7]. Such combination therapy achieves a considerable advantage in median disease-free and overall survival with good toxicity profile in ER+, her-2− breast cancer patients [6, 7]. Among the three clinically available CDKIs, abemaciclib is the most potent agent in preclinical studies, determines a survival advantage in metastatic disease, and has also recently shown a progression-free survival advantage in the adjuvant setting [8, 9]. After oral administration, abemaciclib is mainly excreted via the feces after hepatic metabolism, primarily involving the CYP3A4 cytochrome, while renal excretion is responsible only for 3% of its clearance [10]. Although diarrhea is the most frequent side effect, abemaciclib administration may induce a clinically nonmeaningful increase in serum creatinine as a consequence of the inhibition of inhibited metformin uptake by organic cation transporter 2, multidrug and toxin extrusion (MATE) 1, and MATE2-K transporter, without affecting glomerular function [11]. Although pharmacokinetics and pharmacodynamic data suggest no dose modification for mild to moderate renal insufficiency, the benefit and safety of abemaciclib are uncertain in treating patients with ESRD or those who require maintenance hemodialysis [12–14]. This paper reports the use of abemaciclib plus hormonal therapy in two women with ESRD affected by advanced ER+, her-2− breast cancer to provide a reference for oncologists facing such clinical challenges.

**Cases Report**

After achieving the patient’s informed consent, these 2 cases were sent to the Institutional Review Board for approval. Both patients had been on hemodialysis for years three times a week, and managing medical oncologists deeply discussed the use of a CDKI associated with standard hormonal therapy with both patients and their caregivers. Among the three clinically available CDKIs, physicians picked up abemaciclib for its pharmacokinetic characteristics and openly reported a lack of data concerning the safety and activity of abemaciclib in individuals with end-stage disease to both patients and their caregivers [10, 14]. Before prescription, the oncologist carefully interviewed the patients for concomitant gastrointestinal disorders that could contraindicate abemaciclib use and other drug assumptions. The oncologist performed a drug-drug interaction evaluation employing a drug-checker tool and explained in detail on abemaciclib use to the patients and their caregivers, including written precise suggestions concerning potential side effects. More specifically, the oncologist stressed the precocious use of loperamide and dietary modification in case of diarrhea. He recommended immediately taking loperamide at first or second liquid stool and contacting the medical oncology team via a WhatsApp messenger system. Based on scientific data, the patient with endocrine sensitive ER+, her-2− breast cancer received oral
letrozole 2.5 mg plus abemaciclib 100 mg b.i.d. on a continuous daily schedule. The patient with the resistant disease received fulvestrant 500 mg intramuscularly every 28 days after a loading dose for three times every 2 weeks and abemaciclib 100 mg b.i.d. on a continuous daily schedule. The dosage of abemaciclib was chosen based on data and recommendations present in the medical literature [10, 15]. Oncologists and nephrologists closely monitored both patients for toxicity with monthly visits and via the web for hypoalbuminemia, edema, metabolic acidosis, abnormal enteric movements, or other ESRD-related changes, which could alter the PK profile, increasing the risk of developing other dose-related adverse effects.

Table 1 shows available data on renal function. In addition, hematological and serum chemistry tests were done every 2 weeks during the first 3 months of treatment. Even if not specifically required cardiological function was monitored.

**First Case**

A 68-year-old woman working as a high-school teacher presented progressive breast cancer while taking adjuvant letrozole for 3 years. In February 2018, she was diagnosed with breast cancer and received conservative left breast surgery with axillary dissection after sentinel lymph node analysis positive for cancer. The systemic staging was negative for metastatic disease. Pathology showed a ductal infiltrating carcinoma estrogen receptor 85% progesterin receptor 35%, her-2 score 1, and Ki67 20%. The clinical and pathological stage was pT2, N1, M0. The patients received adjuvant radiation therapy and letrozole. In December 2019, she showed progressive systemic disease at bones and nodes, increasing Ca15-3 documented by PET scan. Besides ESRD, the medical history was not significant. The patient’s performance status was adequate for abemaciclib plus fulvestrant regimen with an Eastern Cooperative Oncology Group Performance Status score of 0, and she received fulvestrant 500 mg intramuscularly on day 1, 14, and 28 and then every 4 weeks plus abemaciclib 100 mg b.i.d. continuously. The patient tolerated the treatment well without severe grade 3 toxicity. After 10 days of treatment with fulvestrant and abemaciclib, the first patient complained of grade 2 diarrhea, according to the National Cancer Institute Common Toxicity Criteria version 5.0. The treating physician called the patient to ensure she followed a correct astringent diet and loperamide assumption. Since intestinal movements remained unchanged, oncologists stopped abemaciclib for 3 days. Then the patients restarted treatment at the dosage of 100

### Table 1. Renal function during treatment with abemaciclib

| Time   | Patient no. 1 | Patient no. 2 |
|--------|---------------|---------------|
|        | CDK-EPI, mL/min/1.73 m² | creatinine, µmol/L | BUN, µmol/L | CDK-EPI, mL/min/1.73 m² | creatinine, µmol/L | BUN, µmol/L |
| 1 month| 3.4           | 962           | 19.1        | 5.6           | 670           | 14.5        |
| 2 months| 3.5          | 932           | 19.0        | 5.8           | 645           | 16.0        |
| 3 months| 3.6          | 908           | 22.7        | 6.4           | 600           | 15.3        |
| 4 months| 3.5          | 921           | 18.7        | 5.7           | 654           | 14.2        |
| 5 months| 3.2          | 1,000         | 19.0        | 5.2           | 705           | 17.1        |
| 6 months| 3.4          | 952           | 25.1        | 5.4           | 690           | 16.0        |
| 7 months| 3.3          | 977           | 22.6        | 5.4           | 668           | 14.7        |
| 8 months| 3.5          | 925           | 19.3        | na            | na            | na          |
| 9 months| 3.9          | 861           | 18.0        | na            | na            | na          |
| 10 months| 3.5         | 943           | 21.4        | na            | na            | na          |
| 11 months| 3.6         | 918           | 22.1        | na            | na            | na          |
mg b.i.d. with moderate grade 1 diarrhea, which disappeared after 2 months of therapy. No electrolyte alterations, interstitial lung disease, or deep vein thrombosis were seen. As shown in Figure 1, restaging of disease showed a partial response. She is under the same treatment after 12 months with no sign of progressive disease.

Second Case
A Caucasian housewife was diagnosed with breast cancer at age 47 years and on June 2014 surgically managed with left quadrantectomy and axillary dissection for ductal infiltrating carcinoma stage pT3, N1, M0, ER 75%, Ki67 50%, Ki67 35%, her-2 0. No chemotherapy was prescribed due to ESRD, and the patient had been treated with adjuvant LHRH and tamoxifen for 5 years. She was therapy and disease-free until February 2021, when a bone scan done for the occurrence of bone pain showed metastatic disease to the spine and left hip. A total body TC scan showed pathological lymph nodes in the left supraclavicular fossa and the base of the neck. The patients had untreated dyslipidemia and mild hypertension well compensated pharmacologically. ECOG patient’s performance status was 1. Since the recurrence free survival was 76 months, she received letrozole 2.5 mg day plus abemaciclib 100 mg b.i.d. continuously. This patient also tolerated the treatment well without severe grade 3 toxicity. Mild grade 1 neutropenia and anemia were recorded after 4 months of treatment but did not require any dose modification. No thrombocytopenia or deep venous thrombosis or interstitial lung disease were noted. The patient has stable disease after 9 months of letrozole plus abemaciclib.

Discussion
The treatment of ESRD and metastatic breast cancer patients may be quite challenging [16, 17]. Unfortunately, data in severe ESRD or patients undergoing hemodialysis are generally limited to single case reports and small case series, making it challenging to draw

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Fig. 1. Restaging of disease with PET scan showing partial response.
scientifically supported conclusions [16, 17]. From a pharmacological point of view, the nonsteroidal type II aromatase inhibitor letrozole is mainly eliminated via renal excretion (90%). In the urine, unmodified letrozole represents only 6%, while most of the drug is found in the form of a glucuronide metabolite (75%) or ketone and carbinol metabolites (9%) [18]. Therefore, no dosage adjustment is required for patients with renal impairment (calculated creatinine clearance: 20–50 mL/min), which does not affect steady-state plasma letrozole concentrations. In addition, the liver mainly clears fulvestrant with less than 1% excreted in the urine [19]. Abemaciclib has the lowest urinary excretion as compared to palbociclib and ribociclib (3% vs. 17–23%), and it is mainly excreted via the fecal route [20]. CDKI4/6 are substrates of the efflux transporter proteins P-glycoprotein and breast cancer-resistance protein present in the proximal tubule cells where they exert their action. These transporters play an essential role in the first-pass elimination of orally administered drugs, excreting them from the systemic circulation at the urine side of the proximal tubules brush border membrane in the kidney [21]. In preclinical models, CDKI4/6 induce epithelial cell cycle arrest and ameliorates cisplatin-induced acute kidney injury, suggesting a potential protective effect on kidneys [22]. In addition, abemaciclib may inhibit renal tubular secretion of creatinine since it inhibits the organic cation transporter 2 and the MATE1/2K pump, which facilitates renal secretion of many cationic drugs [11]. However, the measured glomerular filtration rate and the structural markers of kidney tubular injury (serum and urinary neutrophil gelatinase-associated lipocalin and urinary kidney injury molecule-1) were unmodified during treatment with abemaciclib. To the best of our knowledge, this is the first report of successful treatment with CDKI of metastatic breast cancer in 2 patients with ESRD undergoing hemodialysis. One patient received abemaciclib plus letrozole, and the second one had abemaciclib plus fulvestrant. Abemaciclib was administered with or without food at the starting dose of 100 mg b.i.d., and no dose escalation was done. Both patients showed good response to antihormonal therapy, as shown by PET/CT, and did not report side effects that hampered treatment adherence and drug dose intensity. In these 2 cases, renal function showed no significant variations during treatment with abemaciclib. No signs or symptoms of cardiac or pulmonary disorders were seen.

Conclusions

In conclusion, although data are almost entirely lacking in the medical literature, abemaciclib plus antihormonal therapy in the 2 patients reported in this paper showed good response and safety when treated with abemaciclib plus letrozole or fulvestrant. Mild diarrhea and asthenia are the most likely adverse events when abemaciclib is administered to patients with ESRD or on maintenance dialysis. However, a careful approach is always advisable since this experience may not represent all clinical challenges occurring in breast cancer patients with ESRD. Therefore, in our opinion, it is mandatory to carefully assess patients with ESRD requiring deep cooperation between oncologists, nephrologists, and pharmacists to provide a complete view of risks, benefits, and management of anticancer treatment in these populations.

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Statement of Ethics

The study is exempt from Ethics Committee approval because every diagnostic and therapeutic action for the primary pathology was performed according to the current standards and guidelines. This retrospective review of patients’ data did not require ethical approval in accordance with local/national guidelines. Written informed consent was obtained from both patients for publication of this case report and any accompanying images.

Conflict of Interest Statement

The author declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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Author Contributions

Vittorio Gebbia designed the study concept; drafted the manuscript; contributed to acquisition, analysis, and interpretation of data and critical revision of the manuscript; and read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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