Pneumocystis Pneumonia and Acute Kidney Injury Induced by Everolimus Treatment in a Patient with Metastatic Breast Cancer

Mayuko Nakamura, Ryoichi Matsunuma, Kei Yamaguchi, Ryosuke Hayami, Michiko Tsuneizumi

Department of Breast Surgery, Shizuoka Prefectural Hospital Organization, Shizuoka General Hospital, Shizuoka, Japan

Keywords
Pneumocystis pneumonia · Acute kidney injury · Everolimus · Breast cancer

Abstract
Everolimus, an inhibitor of the rapamycin pathway, is administered with the combination of an aromatase inhibitor for the treatment of metastatic estrogen receptor (ER)-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancers. Interstitial lung disease is a well-known major adverse event associated with everolimus treatment, but it is often difficult to distinguish between interstitial lung disease and Pneumocystis pneumonia, a lung infection. Acute kidney injury is another adverse event that is associated with everolimus use. In this article, we report a case of Pneumocystis pneumonia without respiratory symptoms and acute kidney injury induced by everolimus treatment in a patient with ER-positive and HER2-negative metastatic breast cancer.

Introduction
In patients with nonsteroidal aromatase inhibitor-refractory tumors, the BOLERO-2 trial demonstrated better outcomes with everolimus treatment in combination with the aromatase inhibitor exemestane compared with exemestane monotherapy [1]. Everolimus was approved for estrogen receptor (ER)-positive and human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer therapy on March 17, 2014, in Japan.
Everolimus prevents the phosphorylation of the mammalian target of rapamycin complex 1 (mTORC1), which inhibits the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway. This results in reduced proliferation and escape of aromatase inhibitor-resistant breast cancer cells [2]. It is also widely used as an immunosuppressive agent during transplantations. Everolimus binds to mTOR, which inhibits signal transduction via interleukin-2 and blocks T- and B-cell activation by cytokines [3].

Pneumocystis pneumonia, also known as Pneumocystis jirovecii pneumonia (PCP), is a type of pneumonia that is caused by the yeast-like fungus P. jirovecii. PCP is an opportunistic infection that occurs in immunosuppressed patients [4]. It is more common among patients with acute immune suppression associated with HIV infection, transplant patients receiving immunosuppressant drugs, or cancer patients undergoing chemotherapy.

Nephrotoxicity of mTOR inhibitors has recently been described [5, 6]. The mechanism of mTOR inhibitor-associated nephrotoxicity is thought to involve the impaired recovery of injured tubular epithelial cells, endothelial cells, and mesangial cells [7].

Here we report the case of a patient with metastatic breast cancer who developed PCP and acute kidney injury (AKI) caused by everolimus treatment in combination with exemestane.

**Case Report**

A 63-year-old woman was diagnosed with stage IIA (T2N0M0) breast cancer in her right breast. Immunohistochemistry performed on the primary breast cancer tissue confirmed that the cancer was HER2 negative, 100% positive for ERs, and 100% positive for progesterone receptors. The patient underwent a mastectomy and axillary dissection prior to standard radiation therapy and was subsequently administered anastrozole as adjuvant endocrine therapy.

At the age of 72 years (postoperative year 9), multiple bone, lung, and ipsilateral axillary node metastases were detected. The patient received fulvestrant for 8 months, toremifene for 10 months, and exemestane for 4 months, in this order. Everolimus was added to exemestane therapy following a clinical assessment of exemestane that led to the diagnosis of disease progression based on the identification of several bone, lung, liver, and ipsilateral axillary node metastases at the age of 74 years.

Sixty-six days after the initiation of everolimus and exemestane combination therapy, grade 3 stomatitis, hypovolemia, and body temperature elevation to 38°C were observed, and a partial response in regard to some metastatic sites was achieved. However, the patient was admitted to the hospital on day 69, when CT showed diffuse ground-glass opacity in her bilateral lung field, and her blood test reports were as follows: BUN, 80 mg/dL; Cre, 7.80 mg/dL; LDH, 536 U/L; KL-6, 3,667 U/mL; and β-D-glucan, 38.7 pg/mL. These levels suggested AKI and the presence of interstitial or infectious pneumonia, such as PCP, as a differential diagnosis (Fig. 1).

However, no respiratory symptoms, including cough and dyspnea, were observed. Furthermore, urinary culture and urine cytology indicated no bacterial evidence and no decoy cells, respectively, which are usually found in immunocompromized conditions. In addition to fluids, trimethoprim-sulfamethoxazole and azithromycin were administered to prevent any worsening of the infectious pneumonia, as empirical therapy. A bronchial fibroscope was used and transbronchial lung biopsy (TBLB) performed on day 7 after hospitalization, which identified P. jirovecii cysts, suggesting PCP, not interstitial lung disease (ILD) (Fig. 2).
AKI was considered as drug-induced renal dysfunction, which worsened because of dehydration. Trimethoprim-sulfamethoxazole therapy was continued until normal renal function was restored, and the inflammation was treated, whereas azithromycin was discontinued as soon as *P. jirovecii* cysts were identified. The patient was finally discharged on day 38 after hospitalization (Fig. 3).

**Discussion**

Pulmonary toxicity is a rare but clinically important adverse effect of mTOR inhibitors. Morelon et al. [8] reported 3 cases involving kidney transplant recipients treated with sirolimus in 2000 for the first time. A meta-analysis of five trials involving patients with breast, neuroendocrine, and renal cell carcinoma who were treated with everolimus reported pulmonary toxicity, including infective and noninfective pneumonitis in 10.4% of patients [9]. Thus, this adverse event is now more carefully monitored than before.

ILD is the major adverse drug reaction affecting the respiratory system in patients receiving everolimus therapy [10, 11]. Infiltrative shadows that develop in bilateral lung fields and are observed on a CT scan during everolimus therapy suggest everolimus-induced
ILD. On the other hand, everolimus also has an immunosuppressive effect and can cause opportunistic infections, such as PCP [12, 13]. Because the CT scan results of PCP resemble those of ILD, and elevation of the serum level of KL-6 can be observed in both PCP and ILD, differential diagnosis is a major challenge considering that the treatments for PCP and ILD are very different. The serum β-D-glucan level may be useful for the differential diagnosis, although the diagnostic approach is less specific than microscopic visualization by immunofluorescence staining of induced sputum, bronchoalveolar lavage, or TBLB [14, 15]. In this case, elevation of the serum β-D-glucan level was observed, and *P. jirovecii* cysts were identified with Grocott’s methenamine silver stain of the TBLB sample, which led to the diagnosis of PCP.

Interestingly, respiratory symptoms were not observed, even in the presence of PCP infection in the lungs, while fever elevation and AKI were the major symptoms observed in this case. Considering the fever and renal dysfunction were effectively treated with trimethoprim-sulfamethoxazole, the cause of AKI likely was not only everolimus use; rather, *P. jirovecii* may also have affected renal function.

In this case, no severe adverse events were observed during exemestane treatment alone. Since the combination of everolimus with exemestane induced PCP and AKI, there is a strong possibility that these events were caused by everolimus. In the BOLERO-2 study, AKI was reported in only 1 of the 482 patients with breast cancer, while pneumonia was reported in 13 of the 482 patients [1]. Cases of both events occurring simultaneously are extremely rare.

Patients treated with everolimus have an increased risk of pulmonary toxicity, which could require the interruption of breast cancer treatment. To distinguish ILD and PCP is
difficult, but it is essential, since these diseases are potentially life-threatening and each requires a different therapy. Therefore, microscopic visualization – such as by bronchoalveolar lavage or TBLB, in addition to clinical and radiological aspects – is useful to achieve a definitive diagnosis. Moreover, *P. jirovecii* infections should be considered in cases when severe adverse events such as AKI occur during everolimus treatment, because *P. jirovecii* cannot cause any respiratory symptoms at the initial onset of PCP.

**Acknowledgments**

We would like to thank the staff and nurses for their kind cooperation. We would also like to thank the patient and her family.

**Statement of Ethics**

Informed consent was provided by the patient.

**Disclosure Statement**

The authors have no conflicts of interest to declare.

**Funding Sources**

The authors have no funding source to report.

**Author Contributions**

R. Matsunuma and M. Nakamura wrote the main manuscript. All authors critically reviewed the manuscript for important intellectual content.

**References**

1 Baselga J, Campone M, Piccart M, Burris HA 3rd, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med*. 2012;366(6):520–9.
2 Boulay A, Rudloff J, Ye J, Zumstein-Mecker S, O’Reilly T, Evans DB, et al. Dual inhibition of mTOR and estrogen receptor signaling in vitro induces cell death in models of breast cancer. *Clin Cancer Res*. 2005;11(14):5319–28.
3 Thomson AW, Turnquist HR, Raimondi G. Immunoregulatory functions of mTOR inhibition. *Nat Rev Immunol*. 2009;9(5):324–37.
4 Aliouat-Denis CM, Chabé M, Demanche C, Aliouat EM, Viscogliosi E, Guillot J, et al. *Pneumocystis* species, co-evolution and pathogenic power. *Infect Genet Evol*. 2008;8(5):708–26.
5 Choueiri TK, Je Y, Sonpavde G, Richards CJ, Galsky MD, Nguyen PL, et al. Incidence and risk of treatment-related mortality in cancer patients treated with the mammalian target of rapamycin inhibitors. *Ann Oncol*. 2013;24(8):2092–7.
6 Izzedine H, Escudier B, Rouvier P, Gueutin V, Varga A, Bahleda R, et al. Acute tubular necrosis associated with mTOR inhibitor therapy: a real entity biopsy-proven. *Ann Oncol*. 2013;24(9):2421–5.
7 Fervenza FC, Fitzpatrick PM, Mertz J, Erickson SB, Liggett S, Popham S, et al. Acute rapamycin nephrotoxicity in native kidneys of patients with chronic glomerulopathies. *Nephrol Dial Transplant*. 2004;19(5):1288–92.
8 Morelon E, Stern M, Kreis H. Interstitial pneumonitis associated with sirolimus therapy in renal-transplant recipients. *N Engl J Med*. 2000;343(3):225–6.
Iacovelli R, Palazzo A, Mezi S, Morano F, Naso G, Cortesi E. Incidence and risk of pulmonary toxicity in patients treated with mTOR inhibitors for malignancy. A meta-analysis of published trials. Acta Oncol. 2012;51(7):873–9.

Weiner SM, Sellin L, Vonend O, Schenker P, Buchner NJ, Flecken M, et al. Pneumonitis associated with sirolimus: clinical characteristics, risk factors and outcome – a single-centre experience and review of the literature. Nephrol Dial Transplant. 2007;22(12):3631–7.

Maroto JP, Hudes G, Dutcher JP, Logan TF, White CS, Krygowski M, et al. Drug-related pneumonitis in patients with advanced renal cell carcinoma treated with temsirolimus. J Clin Oncol. 2011;29(13):1750–6.

Bernard V, Lombard-Bohas C, Taquet MC, Caroli-Bosc FX, Ruszniewski P, Niccoli P, et al. Efficacy of everolimus in patients with metastatic insulinoma and refractory hypoglycemia. Eur J Endocrinol. 2013;168(5):665–74.

Saito Y, Nagayama M, Miura Y, Ogushi S, Suzuki Y, Noro R, et al. A case of Pneumocystis pneumonia associated with everolimus therapy for renal cell carcinoma. Jpn J Clin Oncol. 2013;43(5):559–62.

Damiani C, Le Gal S, Da Costa C, Virmaux M, Nevez G, Totet A. Combined quantification of pulmonary Pneumocystis jirovecii DNA and serum (1→3)-β-D-glucan for differential diagnosis of Pneumocystis pneumonia and Pneumocystis colonization. J Clin Microbiol. 2013;51(10):3380–8.

Karageorgopoulos DE, Qu JM, Korbila IP, Zhu YG, Vasilieiou VA, Falagas ME. Accuracy of β-D-glucan for the diagnosis of Pneumocystis jirovecii pneumonia: a meta-analysis. Clin Microbiol Infect. 2013;19(1):39–49.