Case Report

Everolimus-associated Acute Kidney Injury in Patients with Metastatic Breast Cancer

Abstract

Recently, everolimus (Evl) has been introduced in the management of hormone receptor-positive metastatic breast cancer, in combination with aromatase inhibitors. Evl-induced acute kidney injury has hitherto been described in other malignancies, especially renal cell cancer, but only once before in a patient with breast cancer. We describe two cases of Evl-associated nephrotoxicity in patients with breast cancer, one of whom underwent a renal biopsy showing acute tubular necrosis. Both our patients improved after withdrawal of the offending agent and have normal renal functions on follow-up.

Keywords: *Acute kidney injury, acute tubular necrosis, cancer, everolimus, nephrotoxicity*

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Introduction

Mammalian target of rapamycin (mTOR) inhibitors is a recent addition to the treatment of hormone receptor-positive advanced breast cancer, following the pivotal BOLERO-2 trial and subsequent Food and Drug Agency (FDA) approval.[1] These agents are known to ameliorate resistance to endocrine therapies, by suppressing intracellular signaling through the PI3K-Akt-mTOR pathway. Everolimus (Evl) at a dose of 10 mg is given in combination with aromatase inhibitors, either steroidal (exemestane) or nonsteroidal (letrozole, anastrozole). Evl has been reported to cause acute kidney injury (AKI), especially so, in patients with underlying chronic kidney disease (CKD), such as patients with renal cell carcinoma (RCC) after tumor resection.[2] Renal biopsy in some cases has revealed acute tubular necrosis (ATN), with variable recovery of renal function.[3] Evl nephrotoxicity, however, is extremely rare in non-RCC cancers and has been reported only once before[4] in breast cancer. Here, we present two cases of Evl-induced AKI in patients with advanced breast cancer.

Case Reports

Case 1

A 54-year-old normotensive nondiabetic postmenopausal woman, with previous history of hysterectomy, was diagnosed with infiltrating ductolobular carcinoma of the right breast in 2011. She underwent surgery with modified radical mastectomy and right axillary clearance; postoperative histopathology showed pT2N3M0, hormone receptor-positive, and human epidermal growth factor receptor 2/neu (HER2/neu) positive. She received 6 cycles of adjuvant chemotherapy with TAC (docetaxel, adriamycin, and cyclophosphamide) from December 2011 to April 2012. After completion of chemotherapy, external beam radiotherapy (EBRT) was given, with a dose of 50 Gy/25# to the right chest wall and subclavian fossa till June 2012, followed by hormonal treatment with tablet anastrozole 1 mg daily. She remained asymptomatic till February 2014, when she presented with a backache. Magnetic resonance imaging of the whole spine revealed multiple bony metastases, and positron emission tomography-computed tomography (CT) showed lung and liver metastases as well. Then, she was treated with palliative EBRT and second-line chemotherapy with paclitaxel and carboplatin was given till May 2014, but the disease was progressive, with increased pulmonary metastases. Third-line chemotherapy with two cycles of gemcitabine, carboplatin, and zoledronic acid was given till July 2014. Evl at a dose of 10 mg/day, along with exemestane 25 mg/day and zoledronate 4 mg/month was started in August 2014,

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as the patient developed pleural effusion and mediastinal lymphadenopathy while on previous chemotherapy.

At baseline, on October 1, 2015, her serum creatinine (SCr) was 0.87 mg/dl, and estimated glomerular filtration rate (eGFR) (by Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) was 76 ml/min/1.73 m^2. On October 7, she visited the OPD with the complaints of vomiting, malaise, and decreased urine output for 5 days. She had a blood pressure of 100/60 mmHg, pulse rate of 92/min, and the rest of her physical examination was unremarkable. Laboratory results showed a rise in SCr to 5.4 mg/dl. Her hemoglobin was 9.1 g/dl, total lymphocyte count was 8.7 × 10^3/μl, and platelet counts were 230 × 10^3/μl. Evl was stopped, and she was hospitalized. Intravenous fluids were started because of signs of dehydration and AKI. Echocardiography showed normal cardiac function. In the following days, despite rehydration with 1.5 L/day of intravenous sodium chloride, her renal functions continued to worsen. SCr levels peaked at 7.2 mg/dl and she became oliguric with urine output falling to 250 ml/day. A renal ultrasound excluded postrenal causes of acute renal failure and showed normal sized kidneys. Urine and blood cultures remained sterile. Urine microscopy showed 100 mg/dl of proteinuria, rare granular casts, and no dysmorphic erythrocytes with few leukocytes. Because of uremic symptoms, she was started on hemodialysis. By October 18 (day 11 of renal failure), her renal functions started to improve with her SCr falling to 1.49 mg/dl by October 21 and returned to baseline by October 30. No rechallenge of Evl was attempted. She is presently on fulvestrant 500 mg with stable renal function.

Case 2

A 56-year-old woman was diagnosed as stage T4bN0M0 estrogen receptor (ER)-positive infiltrating ductal carcinoma of the left breast in August 2014. Besides, she had well-controlled Type 2 diabetes mellitus and hypertension for last 4 years as comorbidities, for which she was on glimepiride 2 mg, metformin 500 mg, amlodipine 5 mg, and aspirin 75 mg/day. On CT evaluation, she was found to have metastases in bilateral lungs and liver. She received six consecutive 3-weekly cycles of docetaxel 100 mg, epirubicin 80 mg with 4 mg monthly dose of zoledronic acid. After achieving a partial response to therapy, she was shifted to anastrozole 1 mg dose to which Evl 10 mg OD was added in June 2015, and zoledronate was continued.

At baseline, 1 week after starting Evl, on June 30, 2015, her SCr was 0.98 mg/dl, and eGFR was 64 ml/min/1.73 m^2. Two days later, on July 2, SCr rose to 1.9 mg/dl, on routine investigations, while the patient remained asymptomatic. Evl was stopped on the same day. After 1 week, she reported to the hospital with breathlessness, lethargy, and anorexia. On laboratory evaluation, her SCr had risen to 3.95 mg/dl, and she was hospitalized. However, in the next few days, her renal function continued to deteriorate and SCr peaked at 8.85 mg/dl. With uremic symptoms and worsening metabolic acidosis, she was started on hemodialysis. A renal ultrasound excluded obstructive uropathy and showed normal-sized kidneys. A chest X-ray showed bilateral minimal pleural effusions, but no infiltrates suspicious for infection were observed. Urine and blood cultures remained sterile. Urine microscopy showed 2+ proteinuria, 8–10 granular casts and 1–2 dysmorphic erythrocytes, and few leukocytes per high-power field. A 24-h urine collection showed 0.91 g protein excretion/day. Her urine output dropped to 300–400 ml/day, and she remained dialysis dependent. With no recovery of renal functions after almost a month, a renal biopsy was performed. It was reported as ATN [Figure 1]. From August 19, her S. Cr levels slowly started improving, and she became dialysis-independent. Her S. Cr dropped to 1.86 mg/dl by November 4, 2015, and touched a nadir of 1.26 mg/dl on January 9, 2016. No rechallenge of Evl was attempted.

The trend of renal function in both patients in relation to Evl exposure is shown in Figure 2.

Discussion

mTOR inhibitors have come a long way in clinical therapeutics. Rapamycin was discovered from *Streptomyces hygroscopicus* and was initially noted for its antifungal activity.[5] Over the years, mTOR inhibitors have earned a place in the immunosuppression armamentarium in solid organ transplants. While both sirolimus and Evl are known to be associated with posttransplant proteinuria, AKI is quite uncommon. Nevertheless, mTOR inhibitors can cause prolongation of delayed graft function, purportedly, through increased tubular cell apoptosis and defective regeneration of tubular epithelium. This finding has limited the *de novo* use of mTOR inhibitors in the immediate posttransplant period, but these agents are often used to substitute

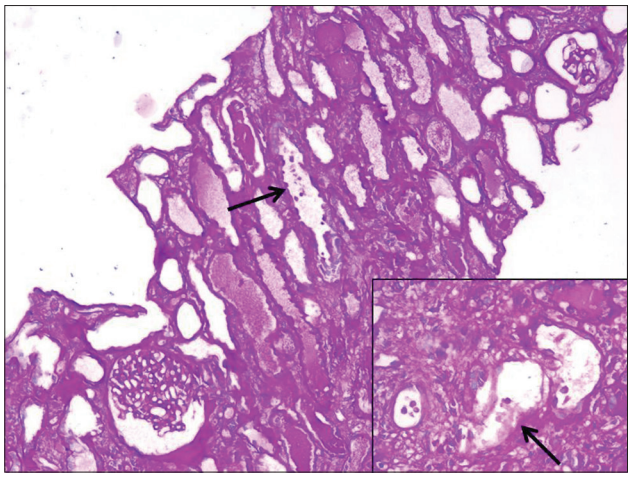

Figure 1: Section from renal biopsy shows unremarkable glomeruli and dilated tubules with detached epithelial cells in tubular lumina (arrow). (H and E, ×100); Inset shows detached necrotic luminal epithelial cells and flattened tubular lining epithelium (arrow). (H and E, ×400)

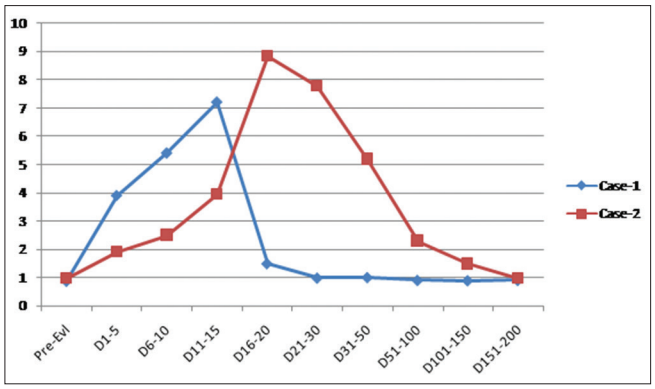

Figure 2: Trend of serum creatinine in the index patients. X-axis - days from everolimus exposure, Y-axis - serum creatinine in mg/dl. Pre-Evl-time before Evl exposure

calcineurin inhibitors in the late posttransplant period, in patients with chronic allograft nephropathy, for their role in preventing tubulointerstitial fibrosis.[6]

In the recent years, mTOR inhibitors have been found to have antitumor effects. mTOR inhibitors have been found to prolong progression-free survival in renal cell cancer and hormone receptor-positive breast cancer, and Evl has been approved by FDA to be used in combination with other agents.[5] Similar observations in kidney transplant recipients, have spurred the use of mTOR inhibitors in patients with posttransplant malignancies, including lymphoproliferative disorders, skin, and visceral malignancies. The dosing strategy of Evl, however, is different in patients on cancer chemotherapy, where a fixed dose of 10 mg/day is used, compared to the much lower starting dose of 0.5–0.75 mg twice a day in transplant recipients (along with trough concentration monitoring).

Nephrotoxicity of mTOR inhibitors has been described very rarely, outside of transplant literature. The mechanism of mTOR inhibitor-associated nephrotoxicity is thought to involve impaired recovery of injured tubular epithelial cells (in delayed graft function and ATN), endothelial cells (thrombotic microangiopathies and glomerulonephritis), and mesangial cells (glomerulonephritis). The impaired cellular regeneration and proapoptotic effect of sirolimus and Evl, is secondary to inhibition of the FKBP12-rapamycin associated protein kinase or mTOR, which is crucial in G1 to S cell-cycle transition. In addition to proteinuric effect, mTOR inhibitors exacerbate proteinuria-mediated tubular toxicity.[7] In 2014, Ha *et al*. published an observational study, in which they noted 14.2% incidence of AKI with Evl administration, almost exclusively in patients with RCC.[2] They observed that deterioration of renal function was associated with underlying CKD (multivariate analysis showed 0.7-fold decreased risk of AKI with 10 ml/m^2/min rise in eGFR). Recently, Evl has been approved for use in hormone receptor-positive HER2/neu negative advanced breast cancer with secondary hormone resistance, following encouraging results from the BOLERO-2 trial. However, unlike in RCC, only one case of Evl-related nephrotoxicity has been published so far. Donders *et al*. described a patient of ER-positive metastatic breast cancer on exemestane and Evl, who developed dialysis-requiring renal failure after 4 weeks of therapy, accompanied by persistent diarrhea, and documented hypotension.[4] Another possible confounding factor in their patient was the concomitant use of simvastatin, which could have led to reciprocal increase in drug levels of both Evl and simvastatin. While the first patient had history of vomiting, which could have led to dehydration, the second patient had no clear inciting factors leading to AKI. It is possible that the eGFR by CKD-EPI equation was an overestimation of renal function, thereby placing these patients at risk of AKI. However, both the index patients were concomitantly receiving an aromatase inhibitor (exemestane in the first case and anastrozole in the second case) and zoledronic acid. Both exemestane and anastrozole are not eliminated by the kidney, and no dose modifications are prescribed in renal failure. While renal failure has not been reported with exemestane, it has rarely been reported with anastrozole, having been associated with glomerular injury in two published case reports, so far (one case of sclerosing glomerulonephritis, and another case of crescentic glomerulonephritis).[8,9] Zoledronate, on the other hand, has been commonly associated with AKI, histologically ATN.[10] Risk factors for zoledronate nephrotoxicity include older age, chronic kidney disease at baseline, previous bisphosphonate use, higher doses, shorter infusion time, and increased dosing frequency. While it is unlikely that the index patient had anastrozole-induced nephrotoxicity (no clinical and laboratory evidence of glomerular involvement as well as in the renal biopsy), contribution of zoledronate to the renal failure cannot be totally ruled out. It can be argued that both the patients had received zoledronate for many months before the onset of renal failure (3 months in the first case and 11 months in the second case), and that the rise in S. Cr correlated temporally with the administration of Evl. One purported mechanism of Evl nephrotoxicity in our patients is that zoledronate had probably caused subclinical renal tubular injury, which was exacerbated by Evl administration, as mTORi may have delayed repair and regeneration of tubular cells, leading to ATN. Similar to our patients, two of the four cancer patients with mTOR inhibitor nephrotoxicity described in the biopsy case series by Izzedine *et al*. were on concomitant zoledronate therapy though none of their patients had breast cancer.[3] Similar to Izzedine *et al*., the biopsy in our patient also showed ATN, and to the best of our knowledge, this is the first reported biopsy of Evl toxicity in a patient with advanced breast cancer.

Conclusion

Evl, an mTOR inhibitor with antitumor activity in breast cancer can cause AKI, histologically characterized by ATN. Renal failure usually responds to stoppage of drug

and supportive management. Nephrologists and oncologists must be aware of this potential complication and must be cautious while using Evl, especially in combination with zoledronate. In additon, consideration must be given to testing efficacy of lower doses of Evl for antitumor activity and drug concentration monitoring to avoid nephrotoxicity.

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Conflicts of interest

There are no conflicts of interest.

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