Acute tubular necrosis associated with mTOR inhibitor therapy: a real entity biopsy-proven

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Background: The protein kinase mTOR (mammalian target of rapamycin) is a critical regulator of cellular metabolism, growth, and proliferation. Inhibitors of mTOR have immunosuppressive and anti-cancer effects, but their effects on the progression of kidney disease are not fully understood. Their most common side-effects include stomatitis, rash, dyslipidemia, hyperglycemia, fatigue, and pneumonitis. However, to the best of our knowledge these agents have not been previously reported to cause severe acute kidney injury (AKI).

Case presentation: We describe four cases of patients with cancer who developed AKI after starting mTOR inhibitor therapy. A kidney biopsy showed acute tubular necrosis (ATN) with prominent tubular dysfunction. Withdrawal of the drug leads to a rapid recovery in two cases. However, a fixed renal dysfunction was noted in the other two cases, one of which will remain dialysis-dependent. Such patients lead to a broad differential diagnosis of AKI including prerenal AKI, ATN, cancer-related GN, and drug-induced acute interstitial nephritis. Accurate history, physical examination, laboratory data, and kidney biopsy are highlighted in establishing the correct diagnosis in such patients.

Conclusions: ATN have not been reported with mTOR inhibitor use. These cases demonstrated a potentially new and serious adverse consequence occurring with the use of an mTOR inhibitor, of which physicians need to be aware.

Key words: acute renal failure, acute tubular necrosis, mTOR
Mammalian target of rapamycin (mTOR), a serine/threonine protein kinase ubiquitously expressed in cells, is a therapeutic target for the cancer treatment arsenal. The mTOR kinase forms a part of two distinct protein complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), which have separate downstream targets and functions. The defining unit of mTORC1 is a rapamycin-sensitive adaptor protein of mTOR and its activation promotes both cell growth and cell proliferation. The defining unit of mTORC2 is a rapamycin-insensitive companion of mTOR, which is not sensitive to rapamycin. Unlike the regulation of mTORC1, little is known about the regulation of mTORC2. The effects of mTORC2 are different from those of mTORC1 and include modulation of cell survival, cell polarity, cytoskeletal organization, and activity of the aldosterone-sensitive sodium channel [1]. Since enhanced activity of the mTOR pathway is frequently observed in malignant cells, inhibition of this kinase has become an attractive strategy to treat cancer. The importance of mTOR in health and diseases has promoted the development of molecules that inhibit mTOR signaling, including rapalogs (sirolimus, temsirolimus, everolimus and deforolimus), which complex with FK506-binding protein 12 to inhibit mTOR complex 1 activity, or the more recent ATP-competitive mTOR inhibitors (mTORis), which target the catalytic site of the enzyme. Rapamycin and its analogs temsirolimus, everolimus, and ridaforolimus referred to as ‘rapalogs’ have demonstrated promising efficacy against renal cell carcinoma and are under investigation for the treatment of other malignancies. However, these mTOR inhibitors produced side-effects that could be unpredictable serious and/or debilitating. Their most common side-effects included stomatitis, rash, hyperglycemia and dyslipidemia, fatigue, and pneumonitis. Furthermore, mTORis are often associated with mild renal impairment and peripheral edema [2].

Acute kidney injury (AKI) is a common clinical problem is associated with substantial morbidity and mortality [3]. Acute tubular necrosis (ATN) occurs in 10% of cases of AKI in the outpatient setting and in 38%–76% of ICU cases of AKI. There are three major causes of ATN: renal ischemia; sepsis; and nephrotoxins. Drugs that cause ATN due to their toxic effects include antibiotics, cytotoxic agents, and others (fosfarnet, pentamidine, acyclovir, indinavir, and radiographic IV contrast). mTOR inhibitors have not been previously reported to cause AKI. We present, to the best of our knowledge, the first cases of ATN after mTOR inhibitor therapy (Table 1).

### case reports

#### case 1

A 57-year-old woman was referred to our nephrology unit because of acute renal failure. She had a history of metastatic (pulmonary, bone) left renal cell carcinoma treated in March 2005 by nephrectomy and renal function zoledronic acid-dosage adjusted, interferon, then sunitinib until 2011 when she had progressive disease. In June 2012, the serum creatinine level was 117 mmol/l (1.33 mg/dl). Everolimus (10 mg daily) was withdrawn in March 2012 after 3 months. After 2 weeks, the patient had developed dysuria and hematuria. The serum creatinine level was 8.03 mg/dL, with a 2.27 mg/dL rise. Renal function recovered after 6 weeks, with a 0.56 mg/dL decrease in serum creatinine.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, year/ Sex</th>
<th>Cancer type</th>
<th>Concomitent nephrotoxic factor</th>
<th>mTOR inhibitor</th>
<th>Serum creatinine before withdrawal</th>
<th>Outcome after drug withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57/W</td>
<td>mRCC</td>
<td>Zoledronic acid</td>
<td>Everolimus</td>
<td>1.33 mg/dl</td>
<td>Renal function recovered (SCr, 2.27 mg/dL) after 6 wks</td>
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<tr>
<td>2</td>
<td>59/W</td>
<td>mNSCLC</td>
<td></td>
<td>TORC1/TORC2 inhibitor 45 mg daily</td>
<td>1.09 mg/dl</td>
<td>Renal function recovered (SCr, 0.87 mg/dL) after 6 wks</td>
</tr>
<tr>
<td>3</td>
<td>56/W</td>
<td>Blymphoma</td>
<td></td>
<td>TORC1/TORC2 inhibitor 45 mg daily</td>
<td>0.56 mg/dl</td>
<td>Renal function recovered (SCr, 0.79 mg/dL) after 10 days</td>
</tr>
<tr>
<td>4</td>
<td>73/M</td>
<td>MCL</td>
<td>Stage IV CKD, FSGS + NAS</td>
<td>Temsirolimus</td>
<td>2.78 mg/dl</td>
<td>Hemodialysis</td>
</tr>
</tbody>
</table>

W, woman; M, man; mRCC, metastatic renal cell carcinoma; mNSCLC, metastatic non-small-cell lung cancer; MCL, mantle cell lymphoma; CKD, chronic kidney disease; FSGS, focal segmental glomerulosclerosis; NAS, nephroangiosclerosis; SCr, serum creatinine.
introduced. The serum creatinine level rose to 132 (1.5 mg/dl), 154 (1.75 mg/dl), 284 (3.22 mg/dl), and 777 (8.83 mg/dl) in August, September, October, and November 2012, respectively, despite everolimus dose reduction (10–5 mg daily). On admission, after 6 months of everolimus, her blood pressure was 140/85 mmHg and she weighed 45 kg. (weight loss, 5 kg).

Physical examination was normal. Laboratory studies revealed a serum creatinine level of 707 µmol/l (8.03 mg/dl), a hemoglobin of 9.1 g/dl, and a platelet count of 390,000/mm³ and a haptoglobin of 4.39 g/l. Urinalysis revealed a daily protein excretion of 0.4 g and 18 red cells per high-power field. The right kidney was normal on non-contrast computed tomography scan and renal sonography. No monoclonal component could be detected in the blood. Circulating immune complexes, antinuclear antibody, rheumatoid arthritis hemaglutinin titer, antitubular basement membrane antibody and antineutrophil cytoplasmic antibody were negative. On renal biopsy, severe tubular necrosis was observed with denudation of tubular basement membranes, cell fragments and red cells in the tubular lumen, and cellular dismorphism (Figure 1a). In the interstitium, mild edema was observed within non-cellular fibrosis. Most of the glomeruli are ischemic. An immunofluorescence study did not show specific deposits. The patient did not require hemodialysis. Everolimus was withdrawn while zoledronic acid maintained. Four weeks after admission, the serum creatinine level was 2.27 mg/dl (200 µmol/l).

**case 2**

A 59-year-old woman was admitted because of acute renal failure. She had a history of metastatic lung adenocarcinoma treated in June 2009 by chemotherapy with cisplatin and pemetrexed. Cisplatin had been stopped in November 2010 and pemetrexed was continued until progression. In May 2011, gemcitabine (four cures) was introduced followed by carboplatin and pemetrexed. In early 2012, frontal metastasis was treated by stereotaxic surgery and radiotherapy. A TORC1/TORC2 inhibitor was initiated on April 2012. She had no previous history of renal disease. The serum creatinine level was 96 µmol/l (1.09 mg/dl) at treatment induction and rises to 185 µmol/l (2.10 mg/dl) and 194 µmol/l (2.20 mg/dl) at weeks 2 and 4, respectively. Treatment was withdrawn. At admission, her blood pressure was 90/60 mmHg (patient’s baseline blood pressure), she weighed 54 kg and physical examination was normal, except discrete lower limbs edema. Laboratory findings revealed: serum creatinine, 179 µmol/l (2.03 mg/dl); hemoglobin, 13.5 g/dl and platelets count 533,000/mm³. Urinalysis revealed a daily protein excretion of 1 g and without white or red cells. Renal sonography showed normal-sized kidneys without abnormalities. Immunological tests were negative. On renal biopsy, severe tubular necrosis was noted. Most tubes are dilated and some of them have denudation of tubular basement membranes, cell fragments and red cells in the tubular lumen, and cellular dismorphism (Figure 1B). The interstitium is free of edema, fibrosis, and inflammation. Most of the glomeruli are ischemic. An immunofluorescence study did not show any specific deposits. Six weeks after the drug withdrawal, the serum creatinine level was 0.87 mg/dl (77 µmol/l).

**case 3**

A 56-year-old woman was referred for acute renal failure. She had a history of mediastinal B lymphoma treated in April 2010 by R-CHOP (eight cycles). Multiple other chemotherapy lines remained inefficient including last gemcitabine and dexamethazone from December 2011 to March 2012. On June 2012, the patient was treated with a TORC1/TORC2 inhibitor. Serum creatinine was 50 µmol/l (0.56 mg/dl) and rises to 115 µmol/l (1.30 mg/dl) 1 week later. Urinalysis revealed a daily protein excretion of 0.5 g and without white or red cells. On admission, her blood pressure was 117/85 mmHg and she weighed 43.3 kg. Physical examination was normal. Renal sonography finding was normal. Immunological tests were negative. On renal biopsy, early mild tubular necrosis was observed. Proximal convoluted tubules sometimes exhibit nuclear effacement and altered epithelial cells with loss of brush border, however, without denudation of tubular basement membranes. The distal tubules are normal. (Figure 1C). Glomeruli, interstitium, and vessels are normal. An immunofluorescence study did not show any specific deposits. A TORC1/TORC2 inhibitor was withdrawn and the serum creatinine level returned to 70 µmol/l (0.79 mg/dl) in 10 days. Six months later, the serum creatinine level was still 0.68 mg/dl (60 µmol/l).

**case 4**

A 73-year-old man was admitted for acute renal failure. He had a history of hypertensive chronic kidney disease (basal serum creatinine level, 200 µmol/l, 2.27 mg/dl). A mantle cell lymphoma diagnosed on February 2009 was treated by chemotherapy (rituximab adriamycin, bortezomib, and dexamethasone, six cycles) replaced by rituximab, dexamethasone, oxaliplatin, and citarabine in August 2010. Temsirolimus as maintenance therapy was introduced in January 2011. The serum creatinine level was 245 µmol/l (2.78 mg/dl) and rises to 406 µmol/l (4.61 mg/dl) 1 month later. On admission, after 5 weeks of temsirolimus, his blood pressure was 180/90 mmHg. Laboratory studies revealed a serum creatinine level of 484 µmol/l (5.5 mg/dl), blood urea of 34 mmol/l, a hemoglobin of 8.6 g/dl and platelets count of 27,000/mm³. Urinalysis revealed a daily protein excretion of 3 g and red 20 red cell per high-power field. Haptoglobin was 1.27 g/l. Renal sonography finding was normal. Immunological tests were negative. The patient required iterative hemodialysis. On renal biopsy, severe tubular necrosis was observed with denudation of tubular basement membranes, cell fragments and red cells in the tubular lumen, and cellular dismorphism (Figure 1D). Superimposed focal segmental sclerosis and nephroangiosclerosis lesions were also noted. In the interstitium, extensive fibrosis (60%) was observed without cellular infiltration. An immunofluorescence study did not show any specific deposits. The patient remained dialysis-dependent. Patients 1, 2, and 3 had no history of diabetes mellitus, hypertension or drug therapy with potential nephrotoxic agents such as nonsteroidal anti-inflammatory drugs, aspirin, angiotensin-targeted agents, and diuretics. Only patient 4 experienced an angiotensin-converting enzyme inhibitor and diuretic treatments related to hypertensive CKD. Moreover, pre-renal and post-renal causes were excluded in all four cases.
We believe that these are the first reports of unexpected acute nephrotoxicity due to mTOR inhibition. Patients with nephrotoxic ATN have a kidney failure phase that typically lasts between 7 and 21 days, although the duration is variable depending upon the length and severity whether or not nephrotoxic therapy is continued. Whereas patients 2 and 3 (with double inhibition TORC1/TORC2) recovered within days after the drug withdrawal, the other two with selective TORC1 inhibition remained renal failed (everolimus for patient 1) or required dialysis (temsirolimus for patient 4) for weeks to months. One can note that AKI was much faster in the case of double blocking mTOR compared with selective TORC1 inhibition, 1 to 2 weeks versus 4 to 12 weeks respectively. So, why kidney damage seems more severe in patients with selective versus double TORC inhibition? Several points can explain this difference in renal damage severity: advanced age and baseline stage IV CKD for patient 4, concomitant zoledronic acid administration (a drug known to cause AKI), and TORC1 inhibitor treatment maintain despite titration. In patients 2 and 3 cases, there was no prior chronic renal disease or nephrotoxic-associated drug, and mTOR inhibitor was stopped very quickly after increase in serum creatinine.

These cases point out that the spectrum of mTOR inhibitor side-effects also includes reversible or not AKI/ATN. Factors predisposing this nephrotoxicity are unknown. However, an irreversible decline in renal function after recovery is more likely in patients over age 65, lower baseline GFR, hypoalbuminemia, and comorbidities including hypertension, heart failure, and current nephrotoxic therapy [4–7]. Not surprisingly, patients with preexisting chronic kidney disease have a higher rate of requiring dialysis when they develop AKI.

mTOR activity is low or absent in the normal kidney, but increased markedly after ischemic injury [1]. Additionally, inhibition of mTOR delays renal recovery and repair. This begs the question of whether mTOR inhibition is the true cause of the renal dysfunction or this is an indirect effect, in not allowing renal tissue repair in response to nephrotoxic stress.

By inhibiting TORC1 (cell growth and cell proliferation) and TORC2 (modulation of cell survival and polarity, cytoskeletal organization, and activity of the aldosterone-sensitive sodium channel) effects, we can assume the consequences on both regeneration of tubular cells and ion transport. Although regulation of protein synthesis is the best understood role of mTORC1, the complex is an important upstream inhibitor of autophagy [8,9]. Indeed, induction of autophagy by everolimus aggravates tubular dysfunction during recovery from kidney injury [10]. Therefore, autophagy appears to be the ‘hypothesis-generating mechanism’ by which mTOR induced ATN.

Drug-induced renal impairment necessitating drug withdrawal is a serious clinical problem. mTORi has been used as an immunosuppressant in transplant medicine, and often immunosuppressant therapy such as calcineurin inhibitors are changed to mTOR-inhibition when there is therapy-induced nephrotoxicity. The dose used in transplant medicine is, however, much lower (e.g. starting dose for everolimus in renal transplantation is usually 0.75 mg oral twice daily, as opposed to 10 mg oral daily in the treatment of metastatic renal cell carcinoma). This may suggest that it is a dose-dependent effect,
and that dose reduction rather than drug withdrawal may be a potential safe option. Oncologists and nephrologists must be aware of this possible side-effect, and we recommend monitoring renal function on a regular basis in cancer patients treated with mTOR inhibitors.

disclosure

The authors have declared no conflicts of interest.

references


Results of treatment of advanced-stage lymphoblastic lymphoma at St Jude Children’s Research Hospital from 1962 to 2002

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Background: Reliable prognostic factors have not been established for advanced-stage pediatric lymphoblastic lymphoma (LL). We analyzed treatment outcomes and potential risk factors in children and adolescents with advanced-stage LL treated over a 40-year period.

Patients and methods: From 1962 through 2002, 146 patients (99 boys and 47 girls) with stage III (n = 111) or stage IV (n = 35) LL were treated at St Jude Children’s Research Hospital. The five treatment eras were 1962–1975 (no protocol), 1975–1979 (NHL-75), 1979–1984 (Total 10 High), 1985–1992 (Pediatric Oncology Group protocol), and 1992–2002 (NHL13). Age at diagnosis was <10 years in 65 patients and ≥10 years in 81.

Results: Outcomes improved markedly over successive treatment eras. NHL13 produced the highest 5-year event-free survival (EFS) estimate (82.9% ± 6.1% [SE]) compared with only 20.0% ± 8.0% during the earliest era. Treatment era (P < 0.0001) and age at diagnosis (<10 years versus ≥10 years, P = 0.0153) were independent prognostic factors, whereas disease stage, lactate dehydrogenase level, and presence of a pleural effusion were not.

Conclusions: Treatment era and age were the most important prognostic factors for children with advanced-stage LL. We suggest that a better assessment of early treatment response may help to identify patients with drug-resistant disease who require more intensive therapy.

Key words: children, adolescent, advanced stage, lymphoblastic lymphoma, prognostic factor, treatment

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