

Case Report



Intolerance to Sunitinib Treatment in Hemodialysis Patients With Metastatic Renal Cell Carcinoma

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Sunitinib is a multiple tyrosine kinase receptor inhibitor that is approved for the treatment of metastatic renal cell carcinoma (RCC). However, neither an appropriate dose nor dosing schedule of sunitinib has yet been established for patients with metastatic RCC who are on hemodialysis. Here, we report on two hemodialysis patients who received sunitinib to treat metastatic RCC. Sunitinib was planned to be administered at a dosage of 25 mg/d for 4 of every 6 weeks. Although sunitinib toxicity was manageable in one patient, disease progression occurred after 4 months of treatment. In the second patient, acute pulmonary edema, caused by uncontrolled hypertension, developed on the 15th day of sunitinib therapy and the drug had to be discontinued. Sunitinib is thus not well tolerated in a hemodialysis setting. Close monitoring of toxicity and dose manipulation may be required if such therapy is attempted.

Keywords: Renal cell carcinoma; Renal dialysis; Sunitinib

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INTRODUCTION

In the setting of metastatic renal cell carcinoma (mRCC), recent advances in the molecular understanding of oncogenic pathways have led to the development of new therapeutic strategies using targeted therapies in an adjuvant setting. Sunitinib is an orally administered inhibitor of tyrosine kinases that targets the vascular endothelial and the platelet-derived growth factor receptors (PDGFRs). Sunitinib, which is approved by the U.S. Food and Drug Administration, currently serves as the standard management of mRCC patients on the basis of data from phase III trials [1]. However, those trials excluded patients with chronic renal failure who were undergoing dialysis. Recently, the sunitinib tolerance and oncologic outcomes of dialysis patients have been explored in several case series [2-5]. The appropriate dose of and dosing schedule for sunitinib have yet to be established in mRCC patients on hemodialysis. In addition, neither long-term treatment outcomes nor the tolerability of sunitinib has been explored in such patients. Here, we report on two patients treated with sunitinib during hemodialysis and the safety issues and oncologic outcomes that we noted.

CASE REPORTS

Case 1

A 57-year-old man underwent right radical and left partial nephrectomy to treat stage III (pT3N0M0) and stage II papillary RCC (pT2N0M0), respectively, in January 2007. Thereafter, his renal function became impaired; his blood urea nitrogen level was 88 mg/mL and his creatinine level was 8.5 mg/mL. Hemodialysis was commenced, three times a week, in May 2007. Three years later, multiple metastatic lesions appeared in the lungs. He also developed additional lymph node metastases in the retroperitoneum and multiple lesions in the liver. Biopsies of the liver masses revealed the presence of mRCC. His prognostic risk category was high, as defined by the Memorial Sloan-Kettering Cancer Center (MSKCC) risk model, with a Karnofsky performance status of 70%, a serum hemoglobin level of 12.1 mg/mL, a serum-corrected calcium level of 10.7 mg/mL, and a serum lactate dehydrogenase (LDH) concentration of 568 U/L. Twenty-five milligrams of sunitinib was administered orally, on a daily basis, for 4 weeks of every 6, commencing in July 2010. Several toxicities, including facial edema, yellowish skin pigmentation, muco-

sitis, hypertension, and general weakness, were manageable (grades 1–2). However, no attempt was made to increase the dose because of a gradual increase in anemia (from grades 1–4) associated with a requirement for frequent packed red blood cell infusion and increasingly problematic chronic fatigue and general weakness. There was no evidence of hypothyroidism. Computed tomography conducted after two cycles of treatment showed that his disease was progressive. Sunitinib was discontinued in November 2010.

Case 2

An 80-year-old female patient underwent left radical nephrectomy after a diagnosis of stage II clear cell carcinoma of the left kidney (pT2N0M0) in 2002. The patient was put on a hemodialysis program (three times per week) 6 years after nephrectomy. Her medical history included essential hypertension, which had been controlled with amlodipine (5 mg/d), for 10 years. In February 2009, she complained of pelvic and lower extremity pain. Abdominopelvic magnetic resonance imaging (MRI) revealed a lytic lesion with dimensions of 7 cm×6 cm at the sacrum. Systemic screening did not reveal any additional metastatic site. Histopathologic evaluation of the lesion showed clear cell RCC metastasis. Although radiotherapy was delivered to the sacrum, the patient was referred to our department for further evaluation because the lytic lesion became enlarged 8 months after radiotherapy. The prognostic risk category was intermediate, as defined by the MSKCC risk model, with a Karnofsky performance status of 90%, a serum hemoglobin level of 10.6 mg/mL, a serum-corrected calcium level of 9.4 mg/mL, and an LDH level of 216 U/L. Twenty-five milligrams of sunitinib was prescribed daily, commencing in March 2010. On the 15th day of treatment, acute pulmonary edema developed as a result of uncontrolled hypertension. Sunitinib could not be continued, but 15 days later, MRI showed that the disease was stable. She refused further oncologic treatment and 10 months after sunitinib withdrawal, she has not developed any new metastatic lesion or progressive disease in the sacrum.

DISCUSSION

Radical nephrectomy is associated with a significant risk of developing chronic kidney disease. Patients with RCC who have undergone nephrectomy can develop chronic renal failure and require hemodialysis more frequently than is the case in normal populations. The long-term treatment outcomes and tolerability of sunitinib in patients on hemodialysis have recently been evaluated in several case series [2–5].

The targets of sunitinib include stem cell factor receptor (Kit), Fms-like tyrosine kinase 3, colony-stimulating factor receptor type 1, glial cell line-derived neurotrophic factor receptor (RET), PDGFR, fetal liver tyrosine kinase receptor 3, and vascular endothelial growth factors 1, 2, and 3 [6]. Sunitinib and its principal metabolite, SU12662, are

eliminated principally in the feces; only 15% to 20% of the drug is cleared by the kidney [7].

Prior reports on patients undergoing chronic hemodialysis suggested that sunitinib treatment was usually well-tolerated when the drug was given at a dosage of 50 mg/d for 4 weeks of every 6 weeks. No pharmacokinetic data were available for our patients; hence, we could not determine whether a change in the elimination kinetics of sunitinib might have increased drug toxicity. However, Izzedine et al. [8] found wide interpatient variability in terms of sunitinib pharmacokinetics in two patients on hemodialysis, but no increase in toxicity was evident. It was concluded that the pharmacokinetic features were similar to those found in patients with normal renal function. Therefore, sunitinib could be administered at any time, regardless of hemodialysis status. However, clinicians treating such patients must closely monitor the side effects of fatigue, hypertension, and cardiac dysfunction, because these toxicities can be exaggerated if sunitinib is prescribed. Sunitinib dose reduction is indicated if significant toxicity develops.

Hypertension is a major side effect of sunitinib. Similarly, hypertension is of concern in dialysis patients and affects up to 72% of such patients [9]. Another very significant side effect of both the drug and dialysis is fatigue. Follow-up data from the phase III clinical trial of sunitinib (compared to γ -interferon) suggested that 21% of patients will develop a left ventricular ejection fraction (LVEF) less than the lower limit of normal. Furthermore, changes in electrocardiographic readings, elevations in cardiac enzyme (creatinine kinase-myoglobin and troponin T) levels, and echocardiographic abnormalities (reduced LVEF and impaired contraction/relaxation) have been documented in such patients [10]. In addition, cardiovascular mortality in patients undergoing dialysis is much higher than that of the general public.

Our patients did not tolerate sunitinib well at a dose of 25 mg per day on 4 weeks out of every 6. Sunitinib treatment aggravated underlying hypertension and general weakness. We were unable to increase the dose to a level higher than that given initially. Thus, sunitinib may not be effective in mRCC patients who are being treated with chronic hemodialysis.

In conclusion, we have described the reactions of two dialysis patients to sunitinib treatment for mRCC. Contrary to recent reports indicating that sunitinib is an effective drug with manageable toxicity in the treatment of patients on chronic hemodialysis, our results indicate that sunitinib may not be well-tolerated in such patients, despite the fact that therapy was commenced with a low daily dose in those undergoing hemodialysis. It is thus important to determine a dose that is both effective and that causes minimal toxicity. Toxicity must be carefully monitored in patients on hemodialysis. Additionally, more extensive collaboration between oncologists and nephrologists is essential to ensure patient safety; future research efforts should focus on this area.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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