Case Reports in Oncology

Case Rep Oncol 2012;5:627–632
DOI: 10.1159/000345694

Published online:
November 21, 2012

ISSN 1662–6575
www.karger.com/cro

Pharmacokinetic/Pharmacodynamic Analysis of a Hemodialyzed Patient Treated with 25 mg of Sunitinib

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Key Words
Tyrosine kinase inhibitor · Sunitinib · Hemodialysis · Renal cell carcinoma · Pharmacokinetics · Pharmacodynamics

Abstract
Sunitinib has been approved for the treatment of advanced and/or metastatic renal cell carcinoma (RCC). Information on the dosage adjustment of sunitinib for patients undergoing hemodialysis is limited. Especially, efficacy and tolerance of sunitinib at a low dose in such patients are not fully understood. Thus, we examined the effect of hemodialysis on the pharmacokinetics, safety and efficacy of 25 mg of sunitinib. The patient was a 66-year-old man diagnosed with RCC and undergoing hemodialysis. He was treated with sunitinib at 25 mg daily for 4 weeks of a 6-week cycle. There were little differences in the $AUC_{0–24\ h}$ of sunitinib and its major active metabolite SU12662 on day 17 (on hemodialysis) and day 18 (off hemodialysis) of the first cycle. The total sunitinib concentration (sunitinib and SU12662) was approximately 50 ng/ml at a steady state in every cycle. The patient's genotype was wild type for *ABCG2* 421C>A, which is associated with increased sunitinib exposure. In the following two cycles of sunitinib, computed tomography scan showed a partial response of the lung metastasis. During the first cycle, the patient developed grade 2 thrombocytopenia and leukocytopenia. After four cycles of treatment, the patient developed grade 3 fatigue and the sunitinib treatment was discontinued. Our patient on hemodialysis could be safely and effectively treated with 25 mg of sunitinib, and a total sunitinib concentration of about 50 ng/ml was maintained. The pharmacokinetics of sunitinib and SU12662 were rarely affected by hemodialysis. Therapeutic drug monitoring could be helpful during sunitinib therapy, especially in a specific population.

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Introduction

Renal cell carcinoma (RCC) is the third most common malignancy of the urinary tract and accounts for almost 3% of adult malignancies [1]. Recent progress in the development of molecular targeted agents has expanded the treatment options for patients with metastatic RCC. Sunitinib is an oral tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor and FMS-like tyrosine kinase 3 receptor. Sunitinib is of benefit for improving progression-free survival significantly in comparison with interferon-α in advanced RCC patients [2]. Most clinical trials indicate renal function impairment as an exclusion criterion. RCC is a complication of chronic kidney disease, and hemodialysis has also been shown to be a risk factor for RCC, with a higher incidence in patients on hemodialysis than in the general population [3]. However, limited data are available on sunitinib usage, especially in patients on hemodialysis. A previous study reported pharmacokinetic (PK) analysis of sunitinib at a standard dose of 50 mg in patients undergoing hemodialysis [4]. As compared to RCC patients in Western countries, Asian patients show higher frequency of adverse events such as thrombocytopenia and hand-foot syndrome. For these reasons, about 80% of Japanese and Korean patients are forced to discontinue or reduce the dose of sunitinib [5, 6]. In these situations, efficacy and tolerance of sunitinib at a low dose in hemodialyzed patients are not fully understood. In this paper, we report for the first time on a RCC patient undergoing hemodialysis with 25 mg of sunitinib using the PK/pharmacodynamic (PK/PD) approach. We also assessed genetic polymorphisms related to the PK of sunitinib.

Case Report

The patient was a 66-year-old man diagnosed with RCC following macroscopic hematuria in August 2007. He underwent radical nephrectomy for clear-cell carcinoma (stage pT1a cN0 cM0, R0, G2>G3) of the right kidney in September 2007. He started chronic dialysis in September 2007. In August 2008, he developed lung metastases and underwent partial lung resection. In March 2010, he developed further lung metastases. In April 2010, he was treated with interferon-α at 3 million units 3 times weekly, which was discontinued in February 2011 because of severe general malaise. In May 2011, lung metastases were increased, indicating progression. In August 2011, he was treated with sunitinib at 25 mg daily for 4 weeks of a 6-week cycle. The Eastern Cooperative Oncology Group performance status was 0. He was classified as being at intermediate risk according to the Memorial Sloan-Kettering Cancer Center risk criteria. His past medical history included hypertension. He had not been administered any medication that inhibited CYP3A4.

Hemodialysis was performed for 4 h, 3 times weekly. An APS-18SA polysulfone dialyzer (surface area 1.8 m^2) with internal shunt was used. The dialysate flow rate was constant at 500 ml/min and the blood flow rate was 230 ml/min.

We evaluated the PK of sunitinib and SU12662 during the course of the first cycle on day 17 (on hemodialysis) and on day 18 (off hemodialysis). After obtaining written informed consent from the patient, blood samples were collected just before administration (0) and then 2, 6, 12 and 24 h after administration. The 4-hour dialysis session started 2 h after administration. Blood samples were collected in sterilized vacuum tubes for serum separation. The samples were centrifuged (1,700 *g* at 4°C for 10 min), and the harvested serum was stored at –20°C. Acetonitrile (1 ml) was added to 500 μl of serum and vortexed thoroughly. After centrifugation at 11,000 rpm for 10 min at room temperature, the supernatant was transferred into propylene tubes and evaporated at 65°C under a nitrogen stream. Sunitinib and SU12662 were measured by high-performance liquid chromatography. The residue was dissolved with 400 μl of phosphate buffer (pH 2.5) and injected into the high-performance liquid chromatography system. Chromatographic separation was carried out under the

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www.karger.com/cro

following conditions. Shim-pack XR-ODS® (75 × 3.0 mm i.d.) column was used. The mobile phase was composed of 72% phosphate buffer (pH 2.5) and 28% acetonitrile. The flow rate was 1.0 ml/min. UV detection was performed at 423 nm. The injection volume was 40 μl at 40°C. The area under the concentration-time curve (AUC) was computed according to the trapezoidal rule. There were little differences in the $AUC_{0-24\,h}$ of sunitinib and SU12662 on day 17 and day 18 during the course of the first cycle (**fig. 1** and **table 1**). In addition, we measured serum trough concentrations of sunitinib and SU12662 at a steady state of each cycle of treatment. Serum total sunitinib concentrations (sunitinib and SU12662) were 50.7 ng/ml on day 28 of the first cycle, 51.2 ng/ml on day 19 of the second cycle and 50.2 ng/ml on day 19 of the third cycle.

Furthermore, in this patient, we assessed genetic polymorphisms related to the PK of sunitinib. Genotyping of single-nucleotide polymorphisms (SNPs) was performed using Custom TaqMan SNP genotyping assays. A previous study reported that *ABCG2* 421C>A was associated with increased sunitinib exposure [7]. The patient's genotype was wild type for *ABCG2* 421C>A.

Following two cycles of sunitinib, computed tomography scan showed a partial response of the lung metastasis with 39% size reduction from that at baseline according to the Response Evaluation Criteria in Solid Tumors (**fig. 2**a, b). During the first cycle, the patient developed grade 2 thrombocytopenia and leukocytopenia and grade 1 hand-foot syndrome according to Common Toxicity Criteria for Adverse Effect v4.0. After four cycles of treatment, he developed grade 3 fatigue and thus sunitinib treatment was discontinued.

Discussion

Both sunitinib and SU12662 are primarily metabolized by CYP3A4 and excreted in the feces, although 16% of the administered dose is eliminated by the kidney. The present study suggests that the PK of sunitinib and SU12662 is not affected by hemodialysis. This result is similar to that reported in hemodialyzed patients treated with 50 mg of sunitinib [4]. This result may be reasonable because the binding levels of sunitinib and SU12662 to human plasma protein in vitro were 95 and 90%, respectively. It has been reported that the PK of other tyrosine kinase inhibitors, such as sorafenib [8] and erlotinib [9], were not affected by hemodialysis because of similar characteristics of sunitinib.

As shown in table 1, maximum serum concentration (C_{max}) and $AUC_{0-24\,h}$ of sunitinib and SU12662 on day 17 were as follows: C_{max}, 45.9 and 12.7 ng/ml, and $AUC_{0-24\,h}$, 984 and 254 ng × h/ml. These values are almost comparable with those reported in patients with normal renal function receiving 25 mg of sunitinib [10]. The reported PK parameters of sunitinib and SU12662 were as follows: C_{max}, 39.5 and 15.2 ng/ml, and $AUC_{0-24\,h}$, 858 and 324 ng × h/ml [10]. This suggests that the PK of sunitinib and SU12662 is not affected by renal function. This result is similar to that reported in hemodialyzed patients treated with 50 mg of sunitinib [4]. In addition, the SNPs related to the PK of sunitinib assessed in this study were shown to be wild type, and the patient did not take any medication to inhibit CYP3A4/5. These backgrounds may contribute to a similar total sunitinib concentration as compared with a previous report.

Sunitinib inhibits VEGFR-2 and PDGF-β phosphorylation in tumor-bearing mice at a total concentration of 50–100 ng/ml of sunitinib (sunitinib and SU12662) [11]. In a clinical trial, Faivre et al. [12] reported that the total sunitinib concentration obtained with a dose of 50 mg daily ranged from 50 to 100 ng/ml. In another clinical trial, Uemura et al. [5] reported that sunitinib was effective at plasma concentrations ≥50 ng/ml in Japanese patients with metastatic RCC. In the present case, escalating dose strategy was planned to apply the dose adjustment, and starting dose was set at 25 mg

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of sunitinib. However, the patient developed grade 2 thrombocytopenia and leukocytopenia during the first cycle. Therefore, the patient continued to be treated with 25 mg of sunitinib throughout the fourth cycle. In this patient, the total sunitinib concentration was approximately 50 ng/ml at a steady state in every cycle, and this patient showed partial response of the lung metastasis after two cycles of sunitinib. These results suggest that therapeutic drug monitoring could be helpful for assessment of the optimal dosage of sunitinib.

In conclusion, our patient on hemodialysis could be safely and effectively treated with 25 mg of sunitinib using the PK/PD approach. The PK of sunitinib and SU12662 was rarely affected by hemodialysis. Therapeutic drug monitoring could be helpful during sunitinib therapy, especially in a specific population. However, this case report is limited in that it refers to a single patient undergoing hemodialysis, and thus further studies are required.

Acknowledgements

This work was supported in part by Grants-in-Aid for Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology.

Table 1. PK parameters and serum concentrations of sunitinib, SU12662 and total drug (sunitinib + SU12662) on day 17 (on HD) and on day 18 (off HD)

	Sunitinib			SU12662			Total drug		
	$AUC_{0-24\,h}$ ng × h/ml	C_{max} ng/ml	t_{max} h	$AUC_{0-24\,h}$ ng × h/ml	C_{max} ng/ml	t_{max} h	$AUC_{0-24\,h}$ ng × h/ml	C_{max} ng/ml	t_{max} h
Day 17 (on HD)	984	45.9	6	254	12.7	6	1,238	58.6	6
Day 18 (off HD)	981	49.9	6	251	11.0	6	1,232	60.9	6

HD = Hemodialysis; t_{max} = Time to C_{max}.

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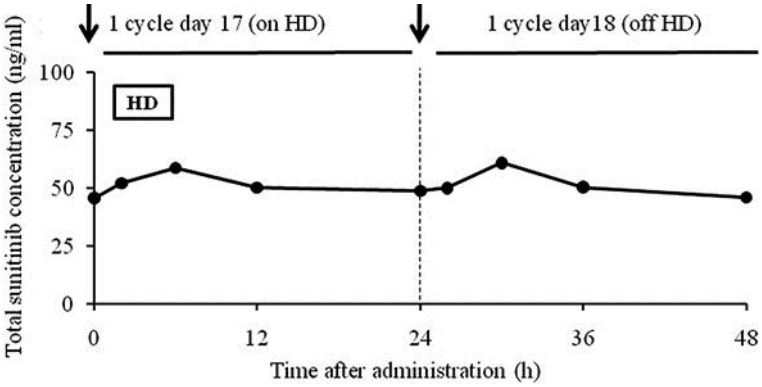

Fig. 1. Plasma concentrations of sunitinib and SU12662 on day 17 (on hemodialysis) and day 18 (off hemodialysis). Arrows indicate administration of 25 mg of sunitinib. The 4-hour dialysis session started 2 h after administration on day 17. HD = Hemodialysis.

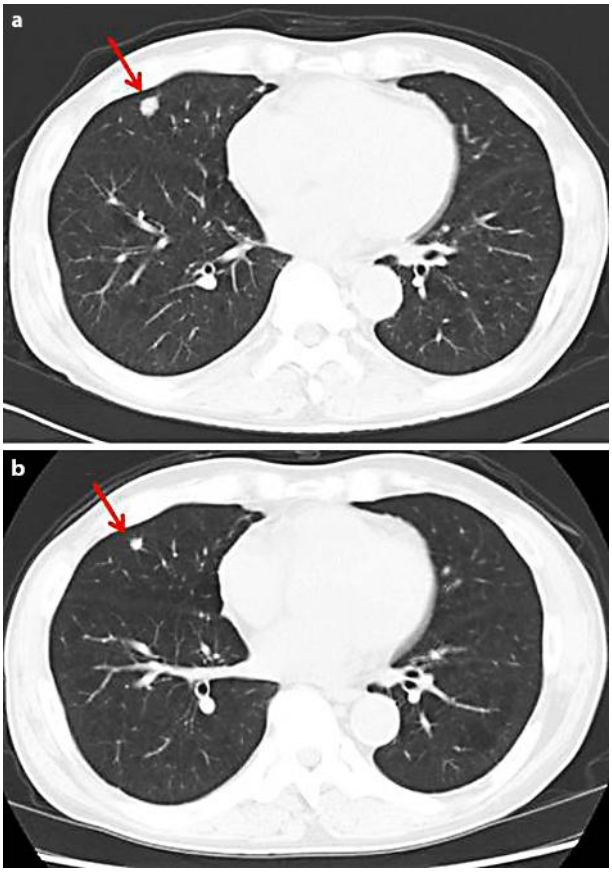

Fig. 2. Tumor responses of lung metastases. Computed tomography scan images of the patient's lungs before administration of sunitinib (**a**) and 2 cycles after initiation of sunitinib (**b**). Arrows point to the metastatic lung lesion.

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