Management of Adverse Events in Patients with Metastatic Renal Cell Carcinoma Treated with Sunitinib and Clinical Outcomes

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Abstract. *Patients with progressive renal cell carcinoma who undergo sunitinib treatment, experience many adverse events (AEs), including thrombopenia and hypertension. Dose reduction or treatment discontinuation due to AEs makes it difficult to control the clinical condition. Therefore, patients' understanding regarding the basics of blood pressure (BP) measurement and how to deal with each AE are particularly important. Here we report whether or not pharmacist instructions help in order to increase patients' awareness of early AE management results in an improvement of treatment outcomes. The present study included 15 patients who were administered sunitinib. From the start of sunitinib treatment, pharmacists continuously provided drug administration guidance to the patients and confirmed their awareness and knowledge regarding AEs, symptom management, and drug adherence. The relative dose intensity (RDI) of 15 patients from week 1 to 24 after sunitinib treatment was calculated. Pharmaceutical interventions significantly improved patients' understanding of BP measurements and reference values, etc. Although the RDI was 67.3%-78.7%, there were no cases of discontinuation of administration or reduction of the dose caused by e.g. hypertension, hand and foot syndrome (HFS) and stomatitis. Pharmaceutical interventions improved patients' awareness of the management of AEs and adherence to sunitinib therapy. As a result, a high RDI was maintained, which may lead to prolonged survival. Therefore, our results suggest that early AE management provided by pharmacists is particularly important to assure the safety and efficacy of sunitinib therapy.*

In clinical trials (1-3) and postmarketing surveillance (4), adverse events (AEs) caused by sunitinib included thrombopenia, hand and foot syndrome (HFS), hypothyroidism, hypertension, and stomatitis. AEs are the main cause for treatment discontinuation (60.0%) of sunitinib in the six weeks after the start of administration (4). According to specific usage surveys by the pharmaceutical company (from the day of approval to August 25, 2011), there were 75 cases of critical hypertension, eight were uncured and two had after effects. Additionally, per the results of a phase II trial in Japan, two cases were reported in which administration was discontinued due to hypertension.

HFS is characterized by flare in the palms and soles and develops to produce severe symptoms such as skin ulcer and blisters, which impairs patients' quality of life (QOL). In addition, stomatitis with painful oral ulceration often leads to inability of oral ingestion. The above AEs that impair QOL are also associated with a reduction in dosage adherence, as well as dosage reduction, or discontinuation of treatment.

It has been shown that sunitinib has inhibitory actions on multiple kinases of growth factor receptors such as platelet-derived growth factor receptors (PDGFR)-α and $-\beta$; vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3; phosphorylation of stem cell factor receptor (KIT), colony-stimulating factor-1 receptor (CSF-1R), and Fms-like tyrosine kinase-3 (FLT-3).

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Figure 1. *Instructions for patients to carry out blood pressure measurements.*

Hypertension caused in patients who undergo treatment with sunitinib, occurs at high frequency, which is associated with VEGFR blockade. Hypertension after treatment with sunitinib is reported to be a useful biomarker that reflects the efficacy of this agent (5). Therefore, management of blood pressure (BP) is considered to be particularly important in order to achieve its anticancer action.

The data on the postmarketing surveillance (4) showed a correlation between the relative dose intensity (RDI) after one cycle (week 6) and both overall survival (OS) and progression-free survival (PFS), suggesting that a good treatment outcome could be expected with the maintenance of a high RDI. Since a high incidence of serious AEs leads to reduced RDI, the management of AEs is important.

At the Aichi Medical University Hospital, sunitinib is administered for the treatment of metastatic renal cell carcinoma (mRCC) on an outpatient basis, with all patients managing their self-care by themselves in their homes. Prior to administration, the pharmacists of the Urology Department provided complete instructions to the patients regarding initial administration. However, most patients could not explain the BP measurement methods and reference values, revealing little knowledge of BP measurement.

In the present study, we investigated whether pharmacist instruction to increase patients' awareness of early AE management has a positive effect on treatment outcomes or not.

Patients and Methods

Patients and treatment. The study was planned to enroll 15 patients diagnosed with mRCC who were administered sunitinib from July 2008 to March 2012 at the Department of Urology in Aichi Medical University Hospital, Japan.

Sunitinib was administered orally at a starting dose of 50 mg once daily. Treatment was given in repeated 6-week cycles consisting of four weeks on therapy, followed by two weeks off (schedule 4/2). Dose reductions or interruptions were permitted to manage AEs according to the guide for proper use of sunitinib by the Pfizer pharmaceutical company. Treatment was continued until either disease progression or withdrawal of treatment. All clinical investigations were approved by the clinical Ethics Committee at Aichi Medical University (12-159), and informed consent for participation was obtained from each patient.

Survey on the awareness and knowledge of patients regarding blood pressure management. During the initial guidance, interviews were conducted to determine the following five items: (i) whether or not BP measurements were being done in the patients' homes; (ii) whether or not the patients had BP measuring equipment; (iii) whether or not the patients correctly understood the BP measurement methods; (iv) whether or not the patients were taking anti-hypertensive drugs; and (v) whether or not the patients understood BP reference values.

Survey on drug compliance. Compliance regarding sunitinib and other drug treatments was confirmed on each day of outpatient care

Check blood pressure values before starting Sutent®
(Pay close attention to blood pressure within 4 weeks after starting Sutent®)

Management of high blood pressure caused by Sutent®

| In cases where high blood pressure is expected | In cases where a quick reduction of blood pressure is needed |

Administration of ARB in the early stage of high blood pressure

ARB + calcium channel blocker (Amlodipine*)

Insufficient effect

Increase up to a maximum dose starting from a minimum dose

If a reduction in blood pressure is still not achieved, consider the combination of multidrug administration or consult a cardiovascular specialist

*The first pass effect of amlodipine is small and the drug interaction with Sutent® is relatively low. Attention to tachycardia.
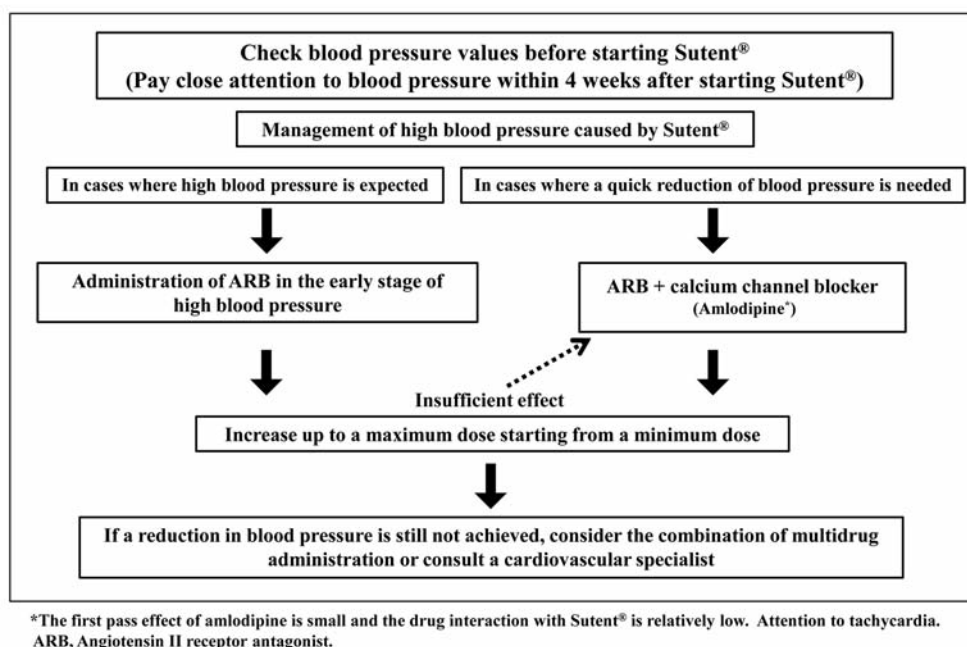ARB, Angiotensin II receptor antagonist.

Figure 2. *Flowchart for physicians to manage hypertension.*

by personal meetings with patients and journals for recording BP data, which were provided by the pharmaceutical industry.

Management of AEs (suggestions and guidance of pharmacists).
Hypertension: Referring to The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009) (6), we created devices describing the BP measurement methods (Figure 1) and reference values. Instruction on the use of these devices was performed at the initial guidance. Patients were also given a pharmaceutical industry pamphlet and the pharmacists continued to provide guidance until the patients could explain the BP measurement methods and the reference values without using any reference materials. The patients were instructed to measure their BP twice (morning and evening) per day every day and record the measured values in a journal provided by the pharmaceutical industry. Furthermore, we continued to confirm whether or not BP measurements were being appropriately carried out and the measurement values recorded in the journals.

BP values were confirmed at the hospital prior to sunitinib administration. For patients with high BP, anti-hypertensive drugs were administered before sunitinib administration in order to control BP. In addition, as a countermeasure against the rise in BP after sunitinib administration, we created drug treatment flowcharts such that any attending physician could easily understand the BP control by drug treatment during outpatient care (Figure 2). Angiotensin II receptor antagonists (ARBs) have been reported to be effective during sunitinib treatment (7) due the mechanism of the rise in BP (8, 9). However, ARBs take some time to be effective, so a combination of ARB and amlodipine (calcium channel antagonist) was given when a blood pressure-lowering effect was needed. Drug selection was made depending on the renal and hepatic function of individual patients.

HFS: At the start of sunitinib administration, preventive HFS countermeasures, such as the application of moisturizers (urea-containing cream or ointment containing heparin-like substance), were suggested to the attending physician as guidance for the patients. For cases in which redness and inflammation of the hands or feet were observed, steroid ointment was recommended early. We continuously provided guidance to apply moisturizers/ointment frequently to limbs daily. Furthermore, we continued to observe the status of the limbs.

Stomatitis: At the start of sunitinib administration, preventive measures against stomatitis including regular gargling with prescription azulene sodium sulfonate was suggested to the attending doctor in order to improve the patients' condition. When there were signs of stomatitis, patients were recommended to switch to gargling with a hospital-prepared lidocaine formulation (saline containing lidocaine and azulene sodium sulfonate). When stomatitis was confirmed, an oral mucosal steroid ointment was adopted. We continuously provided guidance to gargle frequently daily. Furthermore, we continued to observe the oral cavity in order to confirm the presence or absence of expression of stomatitis.

Grade evaluations of all AEs by actual condition surveys and monitoring of hypertension. The BP values during one cycle (six weeks in total, 42 days) for seven out of the 15 patients administered sunitinib (50 mg/day 4/2 schedule) were averaged every seven days from the start of administration up to day 42. Each average value was compared to that of baseline. AEs were monitored at each clinical examination from the start of sunitinib administration to the end of the study.

AEs were graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) version 4.0 (10). Furthermore, we encouraged the pharmacists to listen to the

patients' concerns regarding AEs and treatment on each day of outpatient care and to confirm the journal entries. This extra care was taken to ensure patients felt comfortable with continuing and maintained their level of motivation.

Pharmacist intervention. With respect to the five items in the knowledge survey regarding BP management, the implementation status regarding the management of BP before and after the patients' instruction was comparatively reviewed.

RDI calculation. The dosage and administration of the drug were defined as: the continuous oral administration of 50 mg once per day for four weeks, after which administration is discontinued for two weeks; this comprised one cycle of treatment. A theoretical total dose of 1,400 mg every six weeks was derived, the RDI was calculated as the actual dose delivered as the ratio of the total dose, and the average value was derived for each observation period in 15 cases. In addition, the cause of reduced RDI was also considered.

Statistical analysis. A Chi−square test was applied to confirm comparative evaluations before and after the guidance by the pharmacist regarding BP. The differences in mean BP across time points were tested using repeated ANOVA. Furthermore, Dunnett's test was used for multiple comparisons. Statistical analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC, USA). p-Values for statistical tests were two-tailed and considered to be statistically significant if they were less than 0.05. Overall survival (OS), and progression-free survival (PFS) were calculated using the Kaplan−Meier method (11). Time points for beginning of OS/PFS were defined as the start time of treatment with sunitinib.

Results

Characteristics of patients. Characteristics of studied patients are shown in Table I.

Patients' awareness and knowledge regarding BP management. Fourteen out of 15 patients replied to the question about the management of BP. Eleven patients (78.6%) did not perform BP measurements at their homes, nine (64.3%) had no BP measuring equipment, 13 (92.9%) could not correctly explain the BP measurement method, eight (57.1%) could not explain the BP reference values, and eight (57.1%) did not receive antihypertensive drugs.

After pharmaceutical interventions, all patients obtained a sphygmomanometer and carried out daily recording of BP. Patients also understood well the BP reference values, and a significant improvement effect was found (Figure 3).

Drug adherence. After pharmaceutical interventions, there was no reduction in compliance with sunitinib and other oral remedies found among 15 patients, so pharmacist intervention was continued.

Incidence of AEs associated with sunitinib. As shown in Table II, hematological toxicity occurred in all patients, in which the incidence of grade 3 or more toxicity was 53.4%

Table I. *Characteristics of studied patients.*

Mean age, years (range)	62.2 (47-73)
Mean weight, kg (range)	60.0 (38.0-80.0)
Gender Male/female	12/3
PS (ECOG)	
0/1/2/3	8/5/1/1
MSKCC risk classification	
Favorable/intermediate/poor	2/11/2
Histological subtype	
Clear cell type	11
Non-clear cell type	3
Diagnosis for systemic therapy	
<1 year, n	6
≥1 year, n	8
Common sites of metastases, n	
Lung/lymph nodes/visceral organs/bone/brain	9/7/3/4/1
Starting dose of sunitinib, n	
50 mg/37.5 mg	13/2
First-line population	
(no prior systemic therapy was permitted), n	6
Previous treatment with sorafenib	
after cytokine therapy, n	2
Previous cytokine therapy, n	7
Previous radical nephrectomy, n	14

PS, Performance status; ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan Kettering Cancer Center.

for thrombopenia, 26.7% for neutropenia, and 13.3% for anemia. Grade 3 or more non-hematological toxicities were hypertension (66.7%) and HFS (13.3%).

Figure 4 shows the time course of systolic and diastolic BP during the first cycle of treatment with sunitinib in seven patients who received full-dose sunitinib (50 mg/day) for four weeks. A significant ($p<0.05$) rise in systolic BP was observed on day 14, while diastolic BP was significantly ($p<0.05$) elevated on days 7, 14, and 28.

Rises in BP were successfully controlled by anti-hypertensive drugs. ARB was administered or the dosage was increased at an early stage in three patients; seven patients used a combination of two drugs, including ARB and amlodipine, and one patient was administered amlodipine alone.

Following pharmacist intervention, there were no instances in which sunitinib administration was discontinued due to hypertension as an AE.

On the other hand, all patients used moisturizer for prevention or relief of HFS throughout the study period. When HFS was grade 3, steroid ointment was applied and HFS was improved.

For prevention of stomatitis, all patients continued gargling with azulene sodium sulfonate throughout the study. No stomatitis of grade 3 or more was found, and stomatitis of grade 2 improved with the use of the suggested drugs.
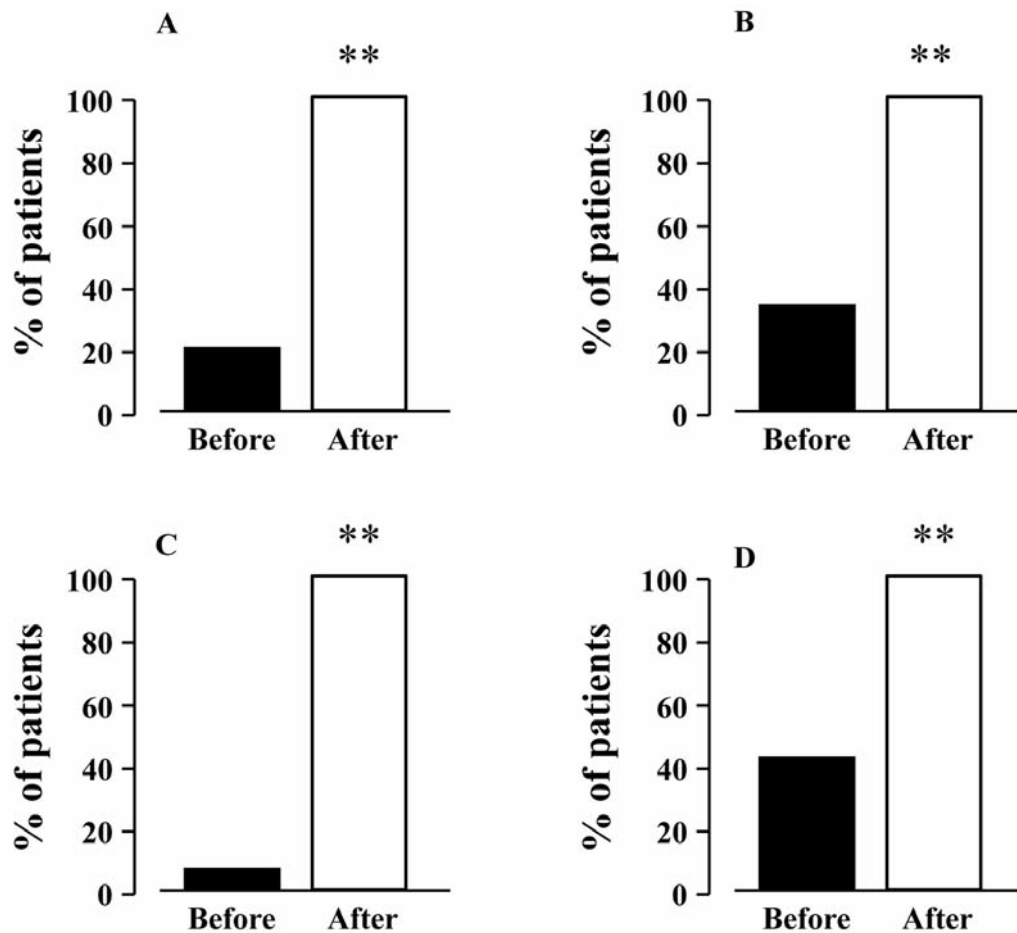
Figure 3. *A comparison of the investigation results before and after pharmacist intervention. A, Patients conducting blood pressure (BP) measurements at home; B, Patients with BP equipment at home; C, Patients with a correct understanding of how to measure BP; D, Patients with a correct understanding of BP reference values.* **Significantly different from before (p<0.001).*

Table II. *Major adverse events and laboratory abnormalities related to sunitinib.*

	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Stomatitis (mucositis)	6 (40.0)	3 (20.0)	0 (0)	0 (0)	9 (60.0)
Hypertension	1 (6.7)	4 (26.7)	10 (66.7)	0 (0)	15 (100)
Diarrhea	8 (53.3)	1 (6.7)	0 (0)	0 (0)	9 (60.0)
Dysgeusia	6 (40.0)	0 (0)	0 (0)	0 (0)	6 (40.0)
Hand–foot syndrome	6 (40.0)	6 (40.0)	2 (13.3)	0 (0)	14 (93.3)
Fatigue	9 (60.0)	6 (40.0)	0 (0)	0 (0)	15 (100)
Hypothyroidism	3 (20.0)	7 (46.7)	0 (0)	0 (0)	10 (66.7)
Anorexia	12 (80.0)	1 (6.7)	0 (0)	0 (0)	13 (86.7)
Thrombopenia	6 (40.0)	1 (6.7)	7 (46.7)	1 (6.7)	15 (100)
Leukopenia	8 (53.3)	7 (46.7)	0 (0)	0 (0)	15 (100)
Neutropenia	9 (60.0)	2 (13.3)	4 (26.7)	0 (0)	15 (100)
Anemia	10 (66.7)	3 (20.0)	2 (13.3)	0 (0)	15 (100)

According to National Cancer Institute Common Terminology Criteria for Adverse events (NCICTCAE). Maximum NCICTCAE grade ver. 4.0 (n=15).
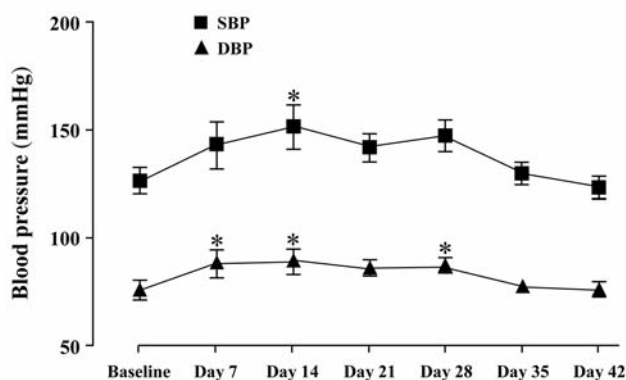
Figure 4. *Changes in the mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) during cycle 1 of sunitinib (50 mg, four weeks on and two weeks off). The baseline of SBP and DBP was 126±6.0 and 74±4.8 mmHg, respectively. *Significantly different from the baseline (p<0.05). Each symbol represents the mean±SE (n=7). When the standard error is small, it is included in the symbol.*

Figure 5. *Relative dose intensity (RDI) during sunitinib treatment. Closed circles and open squares represent the RDI obtained from the present study and postmarketing surveillance (4), respectively.*

RDI calculation. The mean RDI in our study was 75.4%, weeks 1 to 6; 78.7%, weeks 7 to 12; 77.3%, weeks 13 to 18; and 67.3%, weeks 19 to 24, respectively (Figure 5). Two out of 15 patients (13.3%) were administered sunitinib without dosage reduction or treatment discontinuation. Dosage reductions were made due mostly (in eight patients) to thrombopenia (≥grade 3), while other causes of dosage reduction were neutropenia (grade 3), liver dysfunction, pancreatitis, urethral bleeding, and low body weight, which occurred in one patient each. There were no cases in which administration was discontinued or dosage reduced due to hypertension, HFS, or stomatitis alone.

Treatment outcome. As illustrated in Figure 6, the median OS was 28.5 months and the median PFS was 16.4 months.

Discussion

It has been reported for various disease states that improvement in treatment adherence influences control of the clinical condition (12, 13), and that the pharmacist's guidance is important to improve adherence. It has also been reported that the management of AEs is important for continuity of sunitinib treatment (14-16).

In the present study, we showed that adherence improved due to a significant increase in the knowledge and awareness of the patients which occurred as a result of pharmacists' guidance regarding BP management provided to the patients during outpatient visits. The patients were able to continue treatment due to successful management of AEs in the outpatient care setting.

The main causes of the reduction in RDI during treatment with sunitinib were thrombopenia, pancreatitis, and fatigue,
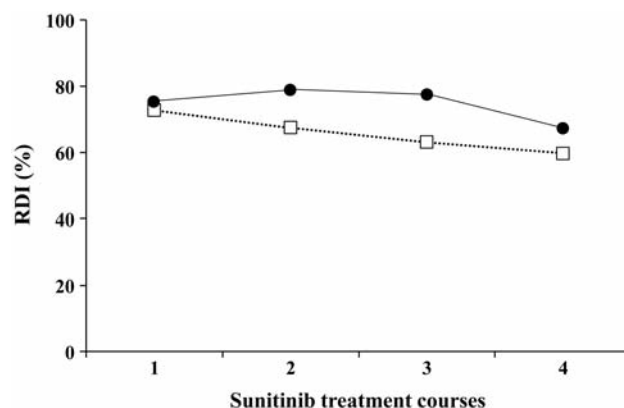
which were unpreventable even if management of the AEs had been continued. In the present study, however, no patients had a reduction in RDI caused by hypertension, HFS, or stomatitis alone. Thus, the relationship between the pharmacist and the patients made it possible to maintain a higher RDI as well as control of the clinical condition, which suggests that the relationship contributed to an extended survival period.

The median OS and PFS were 28.5 months (95% confidence interval: 20.6-∞ months) and 16.4 months (4.0-16.9 months), respectively. Gore and colleagues reported that for patients with mRCC treated with a similar dosage of sunitinib that the median OS and PFS were 18.4 months and 10.9 months, respectively (17). Therefore, prolonged survival was observed in the present study, although we could not compare our data with those reported by Gore and colleagues (17) because of the differences in race and patients' background.

According to the data on the postmarketing surveillance (4), a correlation between RDI after completion of the first course and OS and PFS was found. Therefore, a sufficient treatment outcome could be expected by the maintenance of a high RDI. In addition, PFS was reported to be prolonged in the group of patients treated with sorafenib at high RDI (18). However, our study failed to show a correlation between RDI after one cycle (week 6) and OS and PFS. This may be due to the limited number of enrolled patients. Moreover, the group with ≥70% RDI included poor risk cases [by Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification], brain metastases, pathologically non-clear cell-types, low hemoglobin, and cases of clinical progression less than a year from diagnosis to the start of drug treatment, as well as patients who did not undergo nephrectomy (adverse prognostic factor).
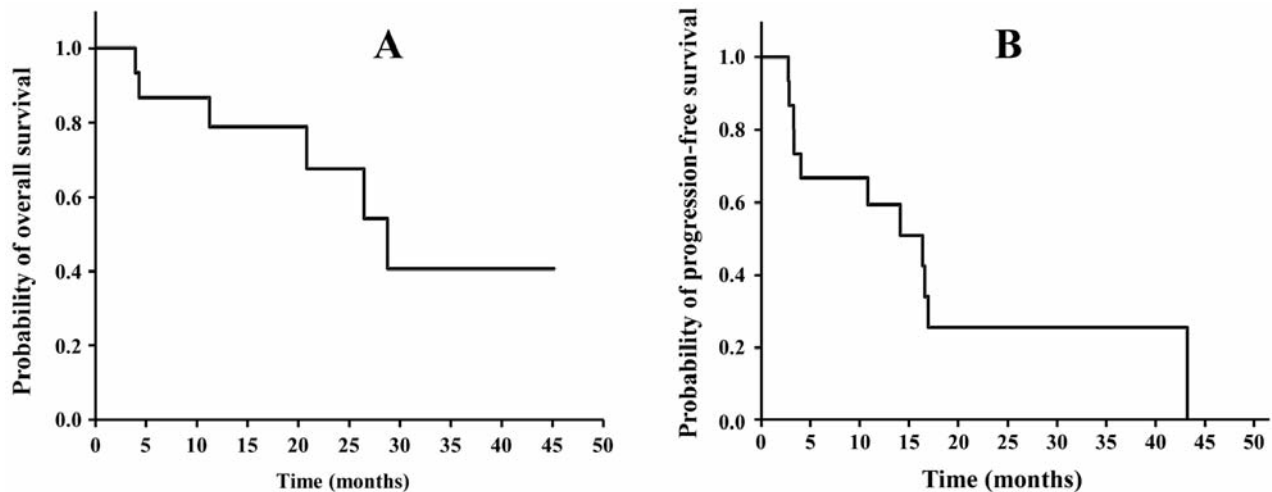
Figure 6. *Kaplan−Meier estimates for overall survival (A) and progression-free survival (B), respectively. The median OS and PFS were 28.5 months (95% confidence interval, CI: 20.6-∞ months) and 16.4 months (95% CI: 4.0-16.9 months), respectively.*

In addition, it has been reported that the area under the plasma concentration−time curve (AUC) of sunitinib contributed to survival extension (19). Therefore, the improvement of adherence by encouragement of the management of AEs is greatly important.

In the present study, the elevation of systolic as well as diastolic BP was observed as early as the first week of the first course of therapy. Therefore, early management of BP should be carried out to minimize the risk of hypertension as an AE. Thus, preparation of the procedure to control the BP may be useful for healthcare professionals, including the attending physicians, in order to reduce the risk of hypertension. Further prospective studies are needed to verify these results.

In our hospital, the pharmacists in the Department of Urology were in charge of pharmaceutical care services to patients in collaboration with the attending physician, which may contribute to a reduction in the physicians' workload. Our results may thus provide insight into early AE management based on pharmaceutical care and contribute to the safety and efficacy of treatment with sunitinib.

Conflicts of Interest

All Authors have declared no conflicts of interest.

Acknowledgements

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