Clinical Importance of Blood Drug Concentration of Oral Molecular Targeted Drugs for Renal Cell Carcinoma

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ABSTRACT -- Purpose: Therapeutic drug monitoring (TDM) is widely used in clinical practice to maximize drug efficacy and minimize toxicities. Currently, it is also practiced in the use of oral molecular targeted drugs. The objective of this study was to assess the clinical importance of measuring the systemic concentration of oral molecular targeted drugs used to treat renal cell carcinoma (RCC). **Methods:** The systemic concentrations of the oral molecular targeted drugs sorafenib, sunitinib, axitinib, pazopanib, and everolimus used for RCC were useful for therapeutic interventions, and clinical outcomes were evaluated retrospectively. **Results:** The interventional use of systemic drug concentration was confirmed in 26 of 87, and their categories are presented. The systemic concentration of sunitinib was useful in dose reduction and/or discontinuation (n = 10), dose escalation (n = 3), and adherence monitoring (n = 2). Nine of the 10 patients whose dose was reduced showed reduced adverse event. Two patients who were intervened in adherence monitor showed improved adherence. For axitinib, dose reduction and/or discontinuation (n = 1) and dose escalation (n = 6) were confirmed. For pazopanib, dose reduction and/or discontinuation (n = 1) and drug interaction detection (n = 1) were confirmed, both of them were confirmed to have reduced adverse events. For everolimus, dose reduction and/or discontinuation (n = 1) and drug interaction detection (n = 1) were confirmed, a patient with reduced dose recovered from adverse events. Interventions for sorafenib were not identified. **Conclusions:** This study demonstrated that systemic concentrations of oral molecular targeted drugs for RCC were considered to be clinically useful for dose adjustment, monitoring of treatment adherence, and the detection of drug interactions. Moreover, this information could be successfully used to guide individualized therapy to maximize the antitumor effects of these drugs.

INTRODUCTION

Renal cell carcinoma (RCC), the most common type of kidney cancer, is widely treated with molecular targeted drugs and immune checkpoint inhibitors (1). Molecular targeted drugs include tyrosine kinase inhibitors (TKI) and mechanistic target of rapamycin inhibitors (mTORi), which show antitumor effects with different modes of action (1, 2). TKIs bind to tyrosine kinases and block the signals that facilitate RCC growth and proliferation, while mTORi block the transfer of phosphates and slow tumor growth (1, 2). In Japan, the TKIs sorafenib, sunitinib, axitinib, pazopanib, and cabozantinib, as well as the mTORi everolimus and temsirolimus are used for RCC treatment (3, 4). Although these targeted drugs show higher objective response rates and significantly prolong median progression-free survival more than other agents, they induce various adverse events such as diarrhea, fatigue, vomiting, myelosuppression, and interstitial pneumonia (5-11).

Therapeutic drug monitoring (TDM) is widely used in clinical practice for maximizing the efficacy and minimizing the toxicities of certain drugs. Recently, TDM has also been recommended and applied to anticancer drug therapy (12-14). TDM of methotrexate for leukemia and fluorouracil for colorectal cancer were reported to improve the clinical outcomes of cancer chemotherapy (15, 16). With oral targeted anticancer drugs, TDM of imatinib, a TKI used for chronic myeloid leukemia, has been recognized to be clinically beneficial for the optimal treatment management of the disease (17-20). Pharmacokinetic/pharmacodynamic (PK/PD) studies of other anticancer drugs have been reported, and additional evidence accumulated in the future may be applicable to future applications of clinical TDM (12-14).

Several PK/PD studies of the oral molecular targeted drugs sorafenib, sunitinib, axitinib, pazopanib, cabozantinib, and everolimus for use RCC therapy in Japan have been reported (14). Serum concentrations of sorafenib in Japanese patients and the area under the curve (AUC) of sorafenib and its metabolite sorafenib *N*-oxide may predict severe adverse effects (21, 22). Sunitinib, which is metabolized by cytochrome P450 (CYP) 3A4 to its active metabolite (*N*-desethyl sunitinib), was evaluated as total sunitinib (sunitinib plus *N*-desethyl sunitinib) (23, 24). The level of sunitinib in the plasma was associated with positive clinical outcomes (23-29), and the target trough level is considered to be 50-100 ng/mL in patients with RCC (26-28).

The AUC of axitinib is associated with both efficacy and the presence of adverse events (30-32). From the PK/PD results of pazopanib, the target trough level is estimated to be 20.5 to 50.3 μg/mL (33, 34). The correlation between the plasma concentration of cabozantinib, the incidence of adverse events, and its antitumor effect is identified using population PK analysis (35). TDM of everolimus is commonly applied for the prevention of organ transplant rejection and treatment of tuberous sclerosis, but its benefit is not clear in cancer (36). An association between systemic levels of everolimus, its toxicity, and its antitumor effects is reported for cancer (37, 38). However, there is insufficient PK/PD data to support routine TDM of oral molecular targeted drugs in the treatment of RCC.

However, measuring the concentration of drugs in the plasma of patients has clinical benefits, including the avoidance of serious adverse events, assurance of efficacy, confirmation of treatment adherence, detection of drug interactions, and elucidation of the effects of other toxic substances when used concurrently (12-14). At our facility, systemic concentrations of sorafenib, sunitinib, axitinib, pazopanib, and everolimus (Table 1) have been measured in patients for their utility in personalized medicine using oral targeted therapies for the treatment of RCC. Hence, in this study, we report the clinical importance of measuring the systemic levels of sorafenib, sunitinib, axitinib, and everolimus in patients with RCC.

METHODS

Patients

The study included patients who received sorafenib, sunitinib, axitinib, pazopanib, and everolimus for the treatment of RCC at Tohoku University Hospital from November 2011 to January 2017. The patients were adults (≥20 years old) with RCC who had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, 2, or 3. This study was performed according to the Declaration of Helsinki. The protocol was approved by the Ethics Committee of Tohoku University Graduate School of Medicine (No. 2010-481-1, 2011-385, 2011-634, 2012-1-444, 2014-1-150, 2015-1-866, and 2020-1-806) and was carried out after obtaining written informed consent from all patients.

Measurement of systemic drug concentration

Systemic drug concentrations (in plasma and blood for TKIs and everolimus, respectively) of both inpatients and outpatients were analyzed using previously reported methods (38-40).

Evaluation of clinical utility

The systemic drug concentrations were measured and reported to their attending physcian and pharmacist. Whenever the intervention was due to the systemic drug concentrations, the outcomes were retrospectively evaluated. The interventions were classified into the following four categories: (i) dose reduction and/or discontinuation, (ii) dose escalation, (iii) adherence monitoring, and (iv) drug interaction detection, all of which were defined as clinically useful (Table 2). In addition, clinical outcomes from interventions based on the plasma drug levels were evaluated retrospectively. PS was evaluated using the ECOG criteria. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE), version 4.0.

RESULTS

A total 87 patients with RCC who were treated with targeted therapies were included in this study, and their baseline characteristics are shown in Table 3. The systemic concentrations of each drug showed a wide variation among the patients. Additionally, interventions based on measurements of systemic drug concentration were conducted in 26 patients, and those for each category and each clinical outcome are presented in Table 4. The plasma concentrations of sunitinib were used to intervene in the treatment by conducting dose reduction and/or discontinuation (n = 10), dose escalation (n = 3), and adherence monitoring (n = 2). Nine of the 10 patients

who were intervened in dose reduction and/or discontinuation confirmed reduction of adverse event. Two patients who intervened in adherence monitor showed improved adherence.

For axitinib, dose reduction and/or discontinuation (n = 1) and dose escalation (n = 6) were confirmed. For pazopanib, dose reduction and/or discontinuation (n = 1) and drug interaction detection (n = 1) were confirmed, both of them were confirmed to have reduced adverse events. For everolimus, dose reduction and/or discontinuation (n = 1) and drug interaction detection (n = 1) were confirmed, a patient with reduced dose recovered from adverse events. Interventions for sorafenib were not identified.

Table 1. Oral molecular targeted drugs for renal cell carcinoma (RCC) used in this study.

Drug	Target molecule	Standard dosage	Major adverse event based on previously reported
Sorafenib	Tyrosine kinase	400 mg twice daily	Diarrhea (43%) Rash or desquamation (40%) Fatigue (37%) Hand–foot skin reaction (30%) Alopecia (27%)
Sunitinib	Tyrosine kinase	50 mg once daily 4 weeks on, 2 weeks off	Diarrhea (43%) Rash or desquamation (40%) Fatigue (37%) Hand–foot skin reaction (30%) Alopecia (27%)
Axitinib	Tyrosine kinase	5 mg twice daily	Diarrhea (55%) Increased creatinine (55%) Hypertension (40%) Fatigue (39%) Hypocalcemia (39%)
Pazopanib	Tyrosine kinase	800 mg once daily	Aspartate aminotransferase increased (61%) Alanine aminotransferase increased (60%) Fatigue (55%) Leukopenia (43%) Thrombocytopenia (41%)
Everolimus	Mechanistic target of rapamycin	10 mg once daily	Anemia (91%) Hypercholesterolemia (76%) Hypertriglyceridemia (71%) Hyperglycemia (50%) Increased creatinine (46%)

Sorafenib (5), sunitinib (6), axitinib (9), pazopanib (10), and everolimus (8) were cited.

Table 2. Categorization of interventions determined by measuring the systemic drug concentration of oral molecular targeted drugs.

Category	**Definition**
Dose reduction and/or discontinuation	Systemic drug concentration was referenced for dose reduction and/or discontinuation
Dose escalation	Systemic drug concentration was referenced for dose escalation
Adherence monitoring	Systemic drug concentration was referenced for adherence monitoring
Drug interaction detection	Systemic drug concentration was referenced for drug interaction detection

Table 3. Patient characteristics at the start of administering each oral molecular targeted drug.

Characteristic Value and (range)	**Sorafenib, n = 5**	**Sunitinib, n = 37**	**Axitinib, n = 23**	**Pazopanib, n = 10**	**Everolimus, n = 12**
Median age, yr	67 (57–73)	64 (30–83)	64 (31–83)	71 (60–81)	64 (32–78)
Male/Female	5/0	26/11	15/8	7/3	7/5
Median weight, kg	57.3 (40.9–63.8)	62.7 (41.0–92.6)	59.6 (39.0–86.8)	58.0 (40.1–65.2)	57.9 (46.0–65.8)
Median BMI, kg/m^2	20.1(17.4–23.6)	23.4(18.4–33.7)	22.7(17.7–29.8)	21.0(18.4–27.7)	21.7(16.3–26.2)
Median AST, IU/L	24 (17–39)	18 (10–46)	24 (14–58)	22 (8–132)	24 (16–45)
Median ALT, IU/L	16 (6–69)	14 (6–104)	15 (10–87)	19 (4–159)	17 (11–53)
ECOG Performance Status, n					
0	5	31	15	7	11
1	0	5	5	0	1
2 or more	0	1	3	3	0
Previous regimens, n					
0	0	31	0	4	0
1	3	3	12	1	2
2	2	2	4	0	8
3 or more	0	1	7	5	2
Initial dose, mg (n)	800 (n = 4)	50 (n = 11)	10 (n = 18)	600 (n = 2)	10 (n = 10)
	600 (n = 1)	37.5 (n = 17)	6 (n = 5)	400 (n = 8)	7.5 (n = 1)
		25 (n = 9)			5 (n = 1)
systemic	3,254	57.5[a]	5.4	20,700	15.2
concentration, Median ng/mL	(559–5,633)	(22.4–196.5)[a]	(0.2–22.0)	(10,600–92,100)	(2.8–28.0)

BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ECOG, Eastern Cooperative Oncology Group; [a]Sunitinib plus its active metabolite *N*-desethyl sunitinib.

Table 4. Effect of interventions by the systemic drug concentration of oral molecular targeted drugs.

Drug	Intervention	Clinical outcome
Sorafenib (n = 5)	None	No change
Sunitinib (n = 37)	Dose reduction and/or discontinuation (n = 10)	Reduced AE (n = 9); No change (n = 1)
	Dose escalation (n = 3)	No change (n = 3)
	Adherence monitoring (n = 2)	Improved adherence (n = 2)
Axitinib (n = 23)	Dose reduction and/or discontinuation (n = 1)	No change (n = 1)
	Dose escalation (n = 6)	No change (n = 6)
Pazopanib (n = 10)	Dose reduction and/or discontinuation (n = 1)	Reduced AE (n = 1)
	Drug interaction detection (n = 1)	Reduced AE (n =1)
Everolimus (n = 12)	Dose reduction and/or discontinuation (n = 1)	Reduced AV (n = 1)
	Drug interaction detection (n = 1)	No change (n = 1)

AE: adverse event.

A case where the measurement of sunitinib concentration in the plasma was useful in predicting adverse events is shown in Figure 1. A 56-year-old female Japanese patient diagnosed with RCC initially underwent a partial left nephrectomy for clear cell carcinoma (cT2N0M0). Four years later, the patient presented with RCC with bone metastasis, and sunitinib therapy was initiated. The patient was prescribed 50 mg sunitinib once daily for a regimen four weeks-on two weeks-off. Her PS, body weight, body mass index (BMI), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and serum creatinine at the start of treatment were 3, 72.8 kg, 32.8 kg/m^2, 16 IU/L, 11 IU/L, and 0.8 mg/dL, respectively. The patient was administered valsartan for hypertension, oxycodone for bone pain, esomeprazole for gastroesophageal reflux disease, and magnesium oxide for constipation. One week after starting sunitinib therapy, the patient experienced grade 1 hand-foot syndrome and grade 1 hypertension. On day 17 of the first course of treatment, sunitinib administration was interrupted because the patient presented with adverse events of grade 3 hypertension, grade 2 thrombocytopenia, and an abnormally high trough total sunitinib (sunitinib plus *N*-desethyl sunitinib) concentration of 196.9 ng/mL, where the target trough range was 50–100 ng/mL (26-28). Despite the withdrawal of sunitinib, the patient exhibited grade 3 thrombocytopenia on day 20 and grade 3 neutropenia on day 24. After recovering from the adverse events, the patient was started on a subsequent course of sunitinib 37.5 mg for 2 weeks-on and 1 week-off. During the second course, the patient experienced grade 3 hypertension, grade 2 neutropenia, and grade 1 thrombocytopenia, and sunitinib trough levels were 120.7 ng/mL on day 15. During the third course, grade 3 hypertension, grade 3 neutropenia, and grade 2 thrombocytopenia were observed. In the next course of treatment, sunitinib was started at a dose of 25 mg and the treatment was continued for the following 2 years.

DISCUSSION

To our knowledge, this study was the first to report the measurement of drug systemic concentration of oral anticancer drugs as an intervention-determining parameter for Japanese patients with RCC. The interventions used in the categories defined in this study were: (1) dose reduction and/or discontinuation, (2) dose escalation, (3) adherence monitoring, and (4) drug interaction detection. The clinical outcomes from these interventions were also investigated and shown to reduce adverse events and improve adherence.

Although sunitinib was effective following dose reduction and treatment withdrawal, the frequency of severe adverse events of sunitinib such as thrombocytopenia, neutropenia, and anorexia was considered high in this study. With a target range of 50–100 ng/mL for plasma sunitinib level (26-28), this was used in 10 of 37 patients to determine the need for dose reduction and/or treatment discontinuation. In one case of a patient treated with sunitinib, as shown in Figure 1, it was inferred that serious adverse events such as bleeding due to thrombocytopenia could be avoided by measuring plasma sunitinib levels. The cause of the high plasma sunitinib concentration of this patient was unclear; however, genetic polymorphisms resulting to changes in the enzymes involved in sunitinib

excretion and the clinical outcome may have affected her sunitinib levels (41, 42). In addition, the abnormally high sunitinib concentration of 196.9 ng/mL observed on day 15 of the first treatment cycle might have been caused by the calcium channel blocker azelnidipine used for sunitinib-induced hypertension. The patient was treated with azelnidipine on days 7–15 for hypertension, after which it was changed to another calcium channel blocker, amlodipine. Calcium channel blockers including azelnidipine exhibit drug interaction with agents metabolized by CYP3A4 (43), and a case where the PK of sunitinib was affected by calcium channel blockers was reported (44). Takasaki et al. (45) reported that delayed excretion of sunitinib

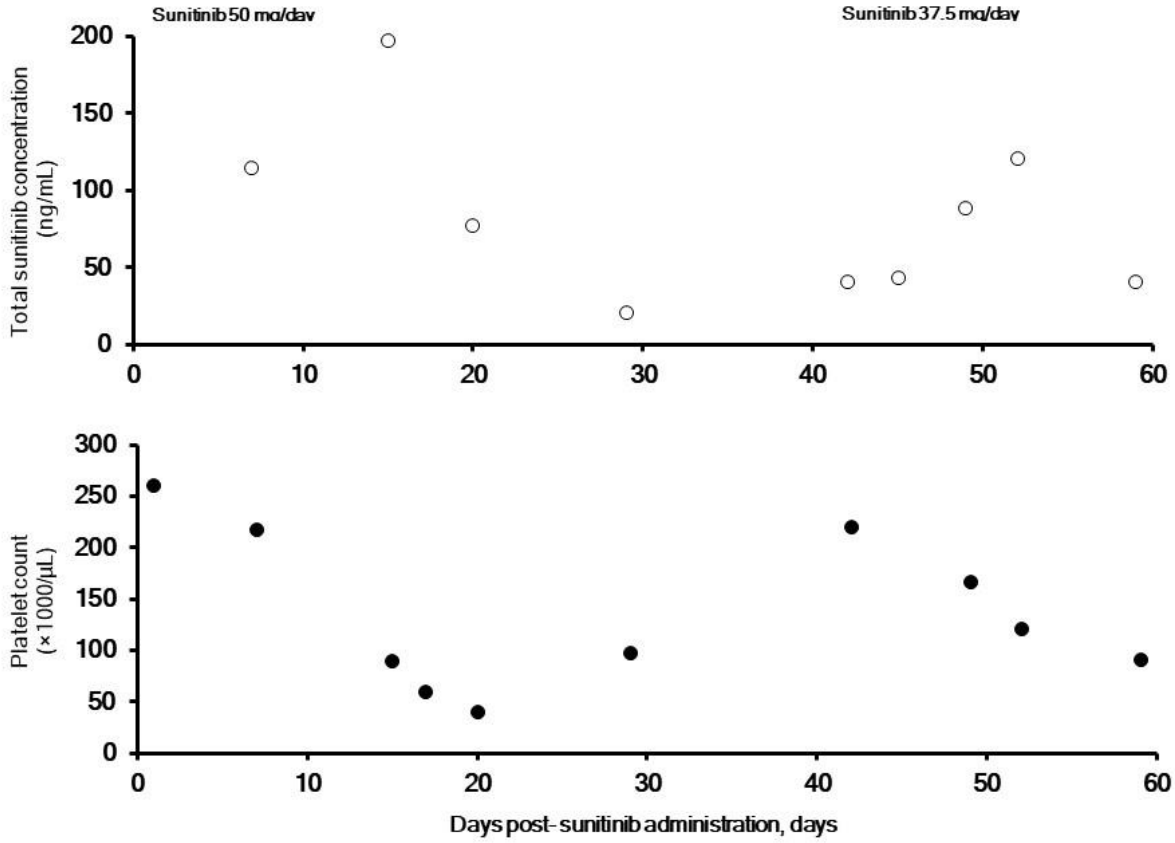

Figure 1. Plasma sunitinib concentrations (sunitinib plus *N*-desethyl sunitinib) and corresponding platelet counts in a patient with an abnormally high trough level of sunitinib and severe thrombocytopenia detected after starting sunitinib therapy.

caused serious adverse events. In addition, this study identified patients in whom no sunitinib was detected in their plasma, and who were later confirmed to have declined taking the drug because of the risk of adverse events. Thus, plasma sunitinib monitoring was useful for confirming abnormally high levels, drug interactions, and treatment adherence. These are important tools that could contribute to the avoidance of the serious adverse events related to sunitinib therapy and improve its therapeutic outcomes, as reported by Takasaki et al. (29).

Axitinib can be started at 5 mg twice daily and can be increased if the patient has no issues with drug tolerability (9). In this study, plasma trough levels of axitinib were used as an indicator of the need for a dose increase in 6 of 23 patients compared to the PK data used in a previously reported study (46). PK/PD studies of axitinib have shown its AUC is an indicator of efficacy and toxicity. (30-32), and this AUC may be more beneficial than trough levels alone as an indicator of clinical outcome. However, because multiple-point systemic sampling is an obstacle to the routine calculation of AUC, its prediction using a limited sampling strategy is

expected to be possible in future.

High plasma levels of pazopanib is associated with adverse events such as hypertension, and its beneficial effects was estimated to appears at > 20.5 μg/mL (33), based on which interventions were performed. In this study, 1 in 10 patients had their plasma levels used to determine the need for dose reduction. Compared with other drugs, there were fewer dose regulation interventions for pazopanib, which could be because its starting dose was lower than the usual 800 mg and the incidence of adverse events was low. In addition, one case that was useful in discovering the drug interaction confirmed in this study has already been previously reported (47). Recently, Noda et al. (34) reported that the effective plasma concentration of pazopanib was in the range of 20.5 to 50.3 μg/mL, and they recommended a dose adjustment to this target range in the future.

TDM of everolimus is common when it is used as an immunosuppressant and, recently, TDM of anticancer drugs was also reported to be useful (36). In this study, the blood concentration of everolimus was indexed at the target concentration of 5–15 ng/mL as for the tumor tuberous sclerosis complex (36, 48). In this study, blood levels of everolimus were used to confirm the need for interventions regarding dose reduction and drug interactions in one patient each, respectively, and these cases have been previously reported (49, 38). In addition, the supporting evidence encourage the routine use of TDM in the future.

The TDM of sorafenib did not show any usefulness in this study, which may have been caused by the small number of cases (n = 5). Shimada et al. (22) reported that in patients with hepatocellular carcinoma, the simultaneous TDM of sorafenib and sorafenib *N*-oxide may be important for the management of adverse events and improve the antitumor effects of the drug.

A limitation of this study was that the evidence was insufficient to support the performance of TDM with drugs other than sunitinib. Moreover, this study was not necessarily constrained to stay within target levels, and we investigated how retrospective analysis of systemic drug concentrations was used in the treatment of RCC. It would be useful to investigate clinical outcomes from patients randomize in both TDM and non-TDM groups.

CONCLUSIONS

This study demonstrated that sytemic concentrations of oral molecular targeted drugs for RCC were considered to be clinically useful for dose adjustment, monitoring of treatment adherence, and the detection of drug interactions. Moreover, this information could be successfully used to guide individualized therapy to maximize the antitumor effects of these drugs.

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CONFLICT OF INTEREST

The authors no conflicts of interest to declare.

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