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Review

Dose Individualization of Oral Multi-Kinase Inhibitors for the Implementation of Therapeutic Drug Monitoring

Satoshi Noda,*[,a] Shin-ya Morita,[a] and Tomohiro Terada[a,b]

[a] *Department of Pharmacy, Shiga University of Medical Science Hospital; Otsu, Shiga 520–2192, Japan: and* [b] *Department of Clinical Pharmacology and Therapeutics, Kyoto University Hospital; Sakyo-ku, Kyoto 606–8507, Japan.*

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Oral multi-kinase inhibitors have transformed the treatment landscape for various cancer types and provided significant improvements in clinical outcomes. These agents are mainly approved at fixed doses, but the large inter-individual variability in pharmacokinetics and pharmacodynamics (efficacy and safety) has been an unsolved clinical issue. For example, certain patients treated with oral multi-kinase inhibitors at standard doses have severe adverse effects and require dose reduction and discontinuation, yet other patients have a suboptimal response to these drugs. Consequently, optimizing the dosing of oral multi-kinase inhibitors is important to prevent over-dosing or under-dosing. To date, multiple studies on the exposure-efficacy/toxicity relationship of molecular targeted therapy have been attempted for the implementation of therapeutic drug monitoring (TDM) strategies. In this milieu, we recently conducted research on several multi-kinase inhibitors, such as sunitinib, pazopanib, sorafenib, and lenvatinib, with the aim to optimize their treatment efficacy using a pharmacokinetic/pharmacodynamic approach. Among them, sunitinib use is an example of successful TDM implementation. Sunitinib demonstrated a significant correlation between drug exposure and treatment efficacy or toxicities. As a result, TDM services for sunitinib has been covered by the National Health Insurance program in Japan since April 2018. Additionally, other multi-kinase targeted anticancer drugs have promising data regarding the exposure–efficacy/toxicity relationship, suggesting the possibility of personalization of drug dosage. In this review, we provide a comprehensive summary of the clinical evidence for dose individualization of multi-kinase inhibitors and discuss the utility of TDM of multi-kinase inhibitors, especially sunitinib, pazopanib, sorafenib, and lenvatinib.

Key words individualized pharmacotherapy; oral multi-kinase inhibitor; dose prediction; therapeutic drug monitoring

1. INTRODUCTION

Oral multi-kinase anticancer agents have been approved for the treatment of diverse types of cancer. These agents have led to improvements in survival, but it is difficult to manage unpredictable therapeutic failure and severe toxicities. One of the reasons for suboptimal therapeutic response and unanticipated toxicity of these drugs is due to failure to select the optimal drug dose, even if the correct drug has been chosen.[1)] Many oral multi-kinase inhibitors are approved at fixed doses regardless of body surface area, body weight, age, or sex. For instance, fixed doses of these drugs could lead to a higher exposure in patients with low body weight and a lower exposure in patients with high body weight. Additionally, organ function, genetic factors affecting activity of metabolizing enzymes and drug transporters, adherence, drug–drug interactions, and drug-food interactions could increase the pharmacokinetic (PK) variation of oral multi-kinase inhibitors.[2)] Indeed, in clinical settings, many oral multi-kinase inhibitors show large inter-patient PK variations at the same dosage of drugs.[3–6)] Thus, the large inter-individual variability in PK and pharmacodynamics (PD) impacting efficacy and safety has been a clinical problem during oral molecular targeted therapy. To overcome these issues, the optimal multi-kinase inhibitor concentration has been determined using a PK/PD approach for a practical therapeutic drug monitoring (TDM) procedure. So far, evidence has accumulated that for some drugs, drug exposure is associated with efficacy or toxicity.[7–9)] TDM of oral multi-kinase targeted anticancer agents could be useful in cases of decreased therapeutic efficacy, unexpected severe side effects, unpredictable suspected poor adherence, or drug–drug or drug–food interactions.[2)] Recently, to clarify the appropriate blood concentration, we attempted to optimize the treatment efficacy of several multi-kinase inhibitors, including sunitinib, pazopanib, sorafenib, and lenvatinib. Among them, sunitinib use is an example of successful TDM implementation. Sufficient data have been published confirming the exposure–efficacy/toxicity relationship of sunitinib, demonstrating that the optimal trough concentration of total sunitinib (sunitinib plus its major active metabolite, SU12662) is 50–100 ng/mL, especially in renal cell carcinoma (RCC) treatment.[10)] Based on this evidence, TDM of sunitinib has been clinically applied to patients with RCC in Japan since April 2018. For other multi-kinase targeted anticancer drugs, exposure-efficacy/toxicity analyses have been reported to determine the optimal concentrations. This review summarizes the concept of PK/PD analysis, exposure-toxicity relationships, and the possibility of PK-guided dose individualization

* To whom correspondence should be addressed. e-mail: snoda@belle.shiga-med.ac.jp

of oral multi-kinase inhibitors, primarily focusing on sunitinib, pazopanib, sorafenib, and lenvatinib.

2. STRATEGIES FOR IDENTIFYING OPTIMAL CONCENTRATIONS OF ORAL MULTI-KINASE INHIBITORS

2.1. Blood Sampling In the field of oncology, TDM has not been established for a variety of reasons. One factor that makes it difficult to apply TDM is the need of a robust sampling strategy.[3] Most of the traditional cytotoxic agents have a very short half-life and are administered by intermittent intravenous injections. Therefore, systemic exposure is best defined by the area under the curve (*AUC*), and in such cases, the collection of multiple timed blood samples is necessary. These requirements are inconvenient and impractical for long-term patient management.

In contrast to cytotoxic agents, most oral multi-kinase inhibitors exhibit a long half-life and are orally administered daily as a monotherapy. Therefore, steady-state trough concentration has the potential to represent systemic exposure. These features resemble those of classical TDM drugs such as immunosuppressants, and the steady-state trough measurements of oral multi-kinase targeted agents might have practical applications in the clinical care of cancer patients. Consequently, trough level monitoring of multi-kinase inhibitors could be useful for applying TDM in routine practical work.

The timing of blood collection for trough concentration is also important in determining the study design.[1] Cancer treatment, including molecularly targeted anticancer drugs, is long-term. The time to show therapeutic effects and side effects vary depending on the cancer type and the characteristics of the therapeutic drug. In this context, it would be difficult to predict all treatment effects and side effects by measuring trough concentrations at only one point. Therefore, serial trough concentration measurement over time will lead to a more accurate analysis of the relationship between blood concentrations and therapeutic effects and side effects of oral multi-kinase inhibitors.

2.2. Markers of Efficacy in Analyzing PK/PD Relationship In oncology, the efficacy endpoint in the short-term is tumor shrinkage. In solid tumors, tumor shrinkage is assessed using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1).[11] Response criteria are as follows: 1) complete response (CR) (disappearance of all target lesions); 2) partial response (PR) ($\geq$ 30% decrease in the sum of diameters of target lesions); 3) stable disease (SD) (neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD)); and 4) PD (at least 20% increase in the sum of diameters of target lesions). Using RECIST 1.1 criteria, the effective concentration range can be statistically determined by comparing the blood drug concentrations of patients who responded to treatment (responders) with those of the patients who did not respond to treatment (non-responders). In general, responders are defined as patients achieving objective response (CR or PR at best response) or disease control status (CR, PR, or SD at best response). Non-responders are defined as patients with PD at the best response.

The long-term efficacy endpoint is the treatment period (time treatment to failure; TTF), progression-free survival (PFS), and overall survival (OS). TTF is defined as the period from the first day of treatment until cessation of treatment due to any cause. PFS is defined as the period from the date of treatment initiation to the date of objective tumor progression or death. OS is defined as the period from the date of treatment initiation until the date of death. For some multi-kinase inhibitors, the correlation of tumor response (objective response or disease control status) with PFS or OS has been demonstrated.[12–15] In that case, tumor response could be a surrogate marker for time-to-event variables (*e.g.*, TTF, PFS, and OS).

2.3. Markers of Toxicity in Analyzing PK/PD Relationships Severe toxicities are crucial issues in multi-kinase targeted anticancer drug treatment, including grade $\geq$3 toxicities according to the Common Toxicity Criteria for Adverse Effects (CTCAE), toxicities requiring dose reduction, interruption or discontinuation, and intolerable toxicities for each patient. The toxic threshold could be determined using a comparative analysis of blood drug concentrations between patients with severe toxicity and those without severe toxicity.

3. SUNITINIB

3.1. Dosage and Administration Sunitinib is an oral multi-kinase inhibitor for vascular endothelial growth factor receptor (VEGFR)-2 and platelet-derived growth factor receptor (PDGFR)-β. Sunitinib is approved for advanced RCC and gastrointestinal stromal tumor (GIST) at a once-daily oral dose of 50 mg on a 4/2 schedule (4 weeks on followed by 2 weeks off).[16,17] Dose reductions of either 37.5 or 25 mg per day are permitted based on individual tolerability, according to the manufacturer's recommendations.

With the advent of sunitinib, the therapeutic outcomes of RCC and GIST have significantly improved; however, the difficulty in adjusting the dosage and administration schedule due to serious adverse events has been a major concern. In a phase III trial for RCC, a total of 38% patients experienced dose reduction due to adverse events, and 32% had a drug interruption.[16] Therefore, 50 mg daily of sunitinib is an overdose for some patients. Unfortunately, in this trial, 21% of the patients had PD or their clinical response could not be evaluated.[16] In these situations, a biomarker for dose adjustment is required.

3.2. Pharmacokinetic Characteristics Sunitinib is extensively metabolized in the liver by CYP3A4, and up to 16% of the drug is excreted in urine.[18,19] The active metabolite SU12662 shows similar pharmacological effects and is metabolized to inactive compounds by CYP3A4.[17] *In vitro*, sunitinib is highly bound to human plasma proteins (95%). The time to maximum concentration (t_{max}) is 6–12 h.[18,20] The half-life of sunitinib is 40–60 h. The PK of sunitinib and SU12662 in patients on hemodialysis (HD) is not altered compared with those in patients with normal renal function. This finding suggests that sunitinib could be safety used in patients on HD without dose adjustment.[21,22] Drug–drug interactions with a CYP3A4 inducer or inhibitor cause notable changes in the *AUC* of sunitinib.[17] Since the solubility of sunitinib does not change below pH 6.8, no effect on sunitinib would be expected during treatment with histamine H_2-receptor antagonists or proton pump inhibitors (PPIs).[23] Additionally, food had no clinically relevant effect on the PK properties of sunitinib and SU12662.[24] However, it should be noted that the *AUC* of suni-

tinib increased by 11% in combination with grapefruit juice, a known inhibitor of intestinal CYP3A4.[25]

3.3. Exposure-Efficacy/Toxicity Relationship The coefficient of variation (CV) of exposure in patients receiving sunitinib at the standard dose of 50 mg/d was reported to be 28–72%, with a large inter-individual variability.[26] Houk *et al.*[27] reported that high sunitinib exposure correlates with cancer shrinkage, but also with increased toxicity, indicating that the efficacy and toxicity of sunitinib are concentration-dependent. In animal studies, it was found that the phosphorylation of VEGFR-2 and PDGFR-β was inhibited at a total blood sunitinib concentration (sum of sunitinib and SU12662) of 50–100 ng/mL.[28] In addition, a phase I study reported that dose-limiting toxicity was frequently observed in patients (three patients) with total sunitinib concentrations ≥100 ng/mL.[20] Based on these findings, we retrospectively assessed the relationship between the blood concentration of sunitinib and the frequency and severity of side effects, TTF, and PFS in patients with RCC in order to determine the optimal concentration of sunitinib.[29] Patients with RCC with a total sunitinib trough concentration of ≥100 ng/mL ($n = 13$) in cycle 1 at steady state (after day 7 of treatment) had a higher frequency of adverse events of any cause of grade ≥3 than those with <100 ng/mL ($n = 8$) (75 *vs.* 23%). Among the patients with ≥100 ng total sunitinib, one patient discontinued treatment because of intestinal perforation. This finding suggests that caution is needed when the total sunitinib concentration is ≥100 ng/mL. Interestingly, this patient with intestinal perforation had variant forms of the intestinal efflux transporters ABCG2 and ABCB1, possibly resulting in elevated sunitinib concentration in intestinal cells. Regarding the exposure-efficacy relationship, the percentage of disease control (CR, PR, or SD at best response) was similar (88 *vs.* 85%) between patients with ≥100 ng/mL and patients with <100 ng/mL. Furthermore, we found that <100 ng/mL total sunitinib was significantly correlated with longer TTF and PFS. These results suggest that total sunitinib concentrations ≥100 ng/mL may shorten the duration of successful treatment due to the development of severe toxicity. In another study, Mizuno *et al.*[30] reported that serious adverse effects occurred at total sunitinib concentrations of ≥90 ng/mL in patients with RCC. Additionally, Nagata *et al.*[31] reported that, by PK model-based analysis, maintaining a total sunitinib trough concentration <100 ng/mL may avoid the onset of grade ≥3 thrombocytopenia. Furthermore, a prospective study showed that PK-guided dose optimization for targeting ≥50 ng/mL of total sunitinib is successful in daily practice for patients with solid tumors.[32]

A recent meta-analysis demonstrated that an alternative dosing schedule, 2 weeks on/1 week off (2/1) schedule, is more effective, as indicated by an improved PFS, than the 4/2 schedule. Moreover, the 2/1 schedule was associated with less severe sunitinib-related toxicity.[33–37] In a recent study, Ito *et al.*[38] reported that the optimal total trough concentration with a 2/1 schedule could be less than 108 ng/mL to reduce severe toxicity induced by sunitinib.

3.4. Target Concentration We have summarized the guidelines for TDM for sunitinib (Table 1). The serum or plasma trough concentration of sunitinib was used to assess sunitinib PK. A semi-physiological PK model for sunitinib and SU12662 reported that the time to reach >90% of the theoretical steady-state concentration was approximately 6 d for sunitinib and 8 d for SU12662.[39] Therefore, we propose that sunitinib and SU12662 trough serum concentrations should be monitored from day 8, targeting 50–100 ng/mL of total sunitinib for RCC. The target range of total trough sunitinib for GIST is not clear, and further PK studies are required.

4. PAZOPANIB

4.1. Dosage and Administration Pazopanib is a multikinase oral molecularly targeted anticancer drug that targets VEGFR, PDGFR, and other tyrosine kinases, and is administered at a standard dose of 800 mg/d once daily. Pazopanib has been approved as a first-line therapy for advanced RCC and as a second-line treatment for non-adipocytic soft tissue sarcoma (STS).[40,41]

Pazopanib has been found to cause serious side effects such as hepatotoxicity, hypertension, thrombocytopenia, anemia, fatigue, and diarrhea in certain patients. In fact, in a phase III study that patients started with 800 mg of pazopanib, 16–24% of patients were reported to have discontinued treatment due to serious side effects of pazopanib.[40] Thus, in clinical practice, the side effects of pazopanib are difficult to predict and often decrease the QOL of patients, which force to reduce or discontinue pazopanib. Therefore, it is necessary for a therapeutic strategy to determine the optimal dosage index of pazopanib.

Table 1. Current Doses, and Target Concentration of Sunitinib, Pazopanib, Sorafenib, and Lenvatinib

Drug	Approved starting dose (Indications)	PK-related PD markers		Proposed target trough concentration
		PK-related efficacy	PK-related toxicity	
Sunitinib	50 mg (RCC, GIST)	Tumor shrinkage[18] TTF,[29] PFS[29]	Neutropenia,[18] Thrombocytopenia,[29] Anorexia,[29] Fatigue[29]	50–100 ng/mL (RCC)[10,29–32,38]
Pazopanib	800 mg (RCC, STS)	Tumor shrinkage,[51] PFS[51,52,56]	Anorexia,[54] Fatigue,[54] Hypertension[53,54]	20–50 μg/mL (RCC, STS)[51,52,54,56]
Sorafenib	800 mg (HCC, DTC)	Tumor shrinkage[72] PFS[75]	Hand-foot syndrome,[72,74] Fatigue,[72] Diarrhea,[72] Rash[72]	1.40–3.45 μg/mL (HCC)[72]
Lenvatinib	24 mg (DTC) 12 mg for body weight ≥60 kg or 8 mg for body weight <60 kg (HCC)	Tumor shrinkage[86,87]	Adverse events of any cause of grade ≥3*.[86]	42–88 ng/mL (DTC)[88] 40–70 ng/mL (HCC)[82,86,87]

PK, pharmacokinetics; PD, pharmacodynamics; RCC, renal cell carcinoma; GIST, gastrointestinal stromal tumor; TTF, treatment to failure; PFS, progression-free survival; STS, soft tissue sarcoma; HCC, hepatocellular carcinoma; DTC, differentiated thyroid cancer. * grade ≥3 anorexia, grade ≥3 fatigue, grade ≥3 hypertension, grade ≥3 edema, grade ≥3 hand-foot syndrome, grade ≥3 stomatitis, and grade ≥3 proteinuria.

4.2. Pharmacokinetic Characteristics Pazopanib is mainly metabolized in the liver by CYP3A4 and excreted in feces, with a renal elimination of <4%. Due to this minimal renal excretion, pazopanib can be used in patients with mild or moderate kidney impairment, or during hemodialysis without dose adjustments.[42,43] In contrast, pazopanib clearance is decreased by 50% in patients with pre-existing moderate hepatic impairment (total bilirubin between 1.5 and 3 times the upper limit of normal). A daily dose of 200 mg is recommended for patients with moderate hepatic impairment. Pazopanib should be avoided in patients with severe hepatic impairment (total bilirubin >3× the upper limit of normal with any elevation of alanine aminotransferase levels). The plasma half-life of pazopanib is 31–35 h.[44,45] *In vitro*, pazopanib is highly bound to human plasma proteins (> 99%), mainly to albumin.[46] Pazopanib should be taken at least 1 h before or 2 h after a meal, because administration of a low- or high-fat meal is associated with a >2-fold increase in the peak serum concentration (C_{max}) and *AUC* of pazopanib.[47] Lubberman *et al.*[48] indicated that a 600 mg dose of pazopanib taken with a continental breakfast is bioequivalent to an 800 mg dose of pazopanib taken in a fasted state. Concomitant use of pazopanib with a PPI, inhibiting gastric secretion for >24 h, resulted in a marked decrease in the absorption and bioavailability of pazopanib.[49,50]

4.3. Exposure-Efficacy/Toxicity Relationship Previous studies have shown a high degree of interpatient variability in pazopanib exposure at the approved initial dose of 800 mg/d, with a CV ranging between 36 and 72%.[26] Several retrospective studies have demonstrated a clear correlation between pazopanib exposure and treatment efficacy. In advanced RCC patients, a previous PK study reported that pazopanib concentrations of ≥20.5 μg/mL at the fourth week of treatment were highly effective.[51] This efficacy threshold was further confirmed in patients with metastatic RCC in a real-life patient cohort.[52] Another study in patients with RCC for adjuvant setting indicated that patients achieving ≥20.5 μg/mL pazopanib had significantly longer disease-free survival.[53] Consistent with the above report in RCC, our study analyzing pazopanib PK showed 88.9% of patients with ≥20.5 μg/mL pazopanib had CR, PR or SD at best response, whereas patients with <20.5 μg/mL had no tumor shrinkage for advanced RCC.[54] Furthermore, Verheijen *et al.*[55] reported that a PK-guided strategy (target trough concentration: ≥ 20.5 μg/mL) for advanced solid tumors resulted in improved treatment efficacy. Recently, Fukudo *et al.*[56] conducted a prospective cohort study to evaluate the benefits of TDM for pazopanib therapy in patients with RCC and STS. In their study, PK-guided dosing targeting a trough level ≥20.5 μg/mL significantly increased median time-to-treatment discontinuation with reduced toxicity and improved overall survival compared to the conventional dosing group. These findings suggest that the PK-guided dose optimization approach of pazopanib could help some patients manage toxicity and improve treatment outcomes.

Regarding pazopanib toxicity, we found that patients who developed grade ≥2 anorexia, fatigue, and hypertension had significantly higher blood levels of pazopanib compared with patients who had grade <2 of these side effects.[54] Furthermore, we reported that pazopanib showed a clinically meaningful association between grade ≥3 adverse events and exposure. To calculate the statistically significant toxicity threshold, we performed receiver operating characteristic (ROC) analysis and found that the significant cut-off value for the occurrence of grade ≥3 adverse effects was 50.3 μg/mL (*AUC*, 0.85; 95% confidence interval (CI), 0.70–0.99; $p < 0.05$). In the group with pazopanib concentration of ≥50.3 μg/mL (13 patients), 8 patients (61.5%) had grade ≥3 adverse reactions, including anorexia, hypertension, thrombocytopenia, anemia, fatigue, and elevated alanine aminotransferase, and a dose reduction was required in 8 patients (61.5%) due to side effects. On the other hand, in the group with pazopanib concentration less than 50.3 μg/mL (14 patients), 1 patient (7.1%) had grade ≥3 adverse reactions, including diarrhea, and a dose reduction was required in 5 patients (35.7%) due to side effects. Verheijen *et al.*[55] have reported that the mean trough concentration of pazopanib was 51.3 μg/mL in patients whose doses were forced to be reduced due to grade ≥3 side effects in a PK-guided study based on pazopanib blood concentration. These observations indicate that a pazopanib trough concentration of >50 μg/mL may be a limiting factor in treatment discontinuation.

Furthermore, we examined the overall response rate (ORR) following pazopanib exposure.[54] ORR was similar between patients with pazopanib concentrations of 20.5–50.3 μg/mL and patients with concentrations of ≥50.3 μg/mL (45.5 *vs.* 46.2%). Therefore, considering the risk of serious side effects and difficulty in continuing treatment with pazopanib concentrations of ≥50 μg/mL, we suggest that the optimal concentration of pazopanib in RCC patients is in the range of 20–50 μg/mL to avoid serious side effects and to ensure efficacy.

4.4. Target Concentration We have summarized the TDM guidelines for pazopanib (Table 1). Pazopanib PK was assessed using the serum or plasma trough concentration of pazopanib. We propose that the pazopanib trough concentration should be monitored from day 8 at a steady state, targeting 20–50 μg/mL for RCC and STS.

5. SORAFENIB

5.1. Dosage and Administration Sorafenib is an oral multi-kinase inhibitor that blocks VEGFR, PDGFR, and stem cell factor receptors. Sorafenib has been approved for the treatment of advanced and/or metastatic hepatocellular carcinoma (HCC), RCC, and thyroid cancer.[57–59] The recommended dosage was 400 mg twice daily. Dose adjustments to 400 mg once daily can be used to manage potential adverse events.

Sorafenib frequently induces early and severe toxicities such as hepatotoxicity, thrombocytopenia, anorexia, fatigue, hand-foot syndrome (HFS), and diarrhea.[60] Because these toxicities are difficult to anticipate and reduce the QOL of patients, dose reduction or discontinuation is required in clinical settings. In fact, treatment was interrupted in 44% of sorafenib-treated patients in pivotal phase III trials of HCC because of severe toxicities, including gastrointestinal adverse events, fatigue, and hepatotoxicity.[58] Consequently, physicians must closely monitor all patients undergoing sorafenib therapy. However, some patients did not respond to sorafenib. In Asia-Pacific trials, 30.7% of patients had PD as the best overall response.[61] However, the clinical parameters that determine the

therapeutic response/safety to sorafenib remain unknown.[62]

5.2. Pharmacokinetic Characteristics Sorafenib is metabolized mainly in the liver by both CYP3A4 and glucuronidation, with urinary excretion representing a minor portion (19%) of the elimination.[63] Sorafenib is almost exclusively bound to plasma proteins (99.5%).[64,65] The plasma elimination half-life of sorafenib is 25–48 h. There was no relevant effect of esomeprazole, a PPI, administration on the PK of sorafenib.[66] This result indicates that sorafenib can be used concomitantly with agents reducing production of gastric acid, such as histamine H_2-receptor antagonists and PPIs. With a high-fat meal, sorafenib bioavailability was reduced by 29% compared with its fasting bioavailability,[67] suggesting that sorafenib is best administered without food or with a light (low-fat) meal.

5.3. Exposure-Efficacy/Toxicity Relationship Previous reports have shown large inter-individual variability,[61,68] which could contribute to the under- or over treatment of sorafenib therapy.

Several studies indicated that the incidence of HFS is concentration-dependent during sorafenib therapy.[69,70] Another report showed that high concentrations of sorafenib are associated with early dermatological adverse events.[71] Our exposure–toxicity analysis showed an association between sorafenib concentration and grade ≥2 occurrences of fatigue, diarrhea, HFS, and rash.[72] Additionally, our findings indicated that the trough sorafenib concentration is significantly higher in patients with grade ≥3 toxicity than in those without grade ≥3 toxicity. This result is consistent with previous PK studies in patients with HCC, in which the increased sorafenib exposure is significantly associated with grade 3–4 adverse events.[70,73] To determine the threshold concentration, we conducted exposure-toxicity analysis for HCC, and our results indicated that a sorafenib trough concentration of ≥3.45 μg/mL is a threshold for grade ≥3 toxicity of sorafenib in patients with HCC.[72] In the multivariate logistic regression analysis, sorafenib concentration ≥3.45 μg/mL was the only parameter independently associated with an increased risk of any grade ≥3 toxicities induced by sorafenib (OR, 10.9; 95% CI, 1.01–117; $p < 0.05$). Dose reduction and treatment discontinuation tendency was greater in patients with ≥3.45 μg/mL sorafenib than in patients with <3.45 μg/mL sorafenib because of toxicities. The most common serious adverse event in patients with ≥3.45 μg/mL sorafenib was liver dysfunction (grade 3 aspartate aminotransferase elevation, 44.5%; grade 3 alanine aminotransferase elevation, 54.5%). Additionally, Karovic *et al.*[74] reported an increase in the incidence of HFS and diarrhea when the minimum blood concentration exceeded 5 μg/mL in patients with solid tumors, suggesting that a high sorafenib trough concentration may be an influencing factor in adverse events.

The exposure-efficacy analysis showed that the mean trough sorafenib concentration was significantly higher in responders (CR, PR, or SD at 3 months) than in non-responders.[72] Based on the ROC curve, the efficacy threshold value of the trough sorafenib concentration predicting good response was 1.40 μg/mL (*AUC*, 0.97; 95% CI, 0.97–1.00; $p < 0.05$). In multivariate analysis, sorafenib concentration and Child-Pugh B classification were important independent factors associated with OS. Regarding sorafenib exposure, there was a significant improvement of OS in the 1.40 μg/mL ≤ sorafenib <3.45 μg/mL group compared with the <1.40 μg/mL sorafenib group (HR, 8.70; 95% CI, 2.07–36.5; $p < 0.01$). There was a trend toward an improved OS in the 1.40–3.45 μg/mL group compared with the ≥3.45 μg/mL sorafenib group (HR, 3.46; 95% CI, 0.94–12.7; $p = 0.06$). In another study, Fukudo *et al.*[75] showed that patients with HCC on a maximal concentration of sorafenib ≥4.78 μg/mL (cut-off value for predicting grade 2≥ hypertension) had prolonged OS than HCC patients with <4.78 μg/mL (median 12.0 *vs.* 6.5 months; $p = 0.0824$). Recently, PK-guided dosing of oral sorafenib in pediatric patients with HCC has been reported to be useful for reducing HFS and maintaining targeted $AUC_{0\text{-}12}$ (20–55 h μg/mL) using simulated PK data.[76]

5.4. Target Concentration We have summarized the guidance of TDM for sorafenib (Table 1). Sorafenib PK was assessed using the serum or plasma trough concentration of sorafenib. We propose that the sorafenib trough concentration should be monitored from day 8 at a steady state. Our results showed that 1.40–3.45 μg/mL sorafenib trough concentration may be the optimal range for HCC. The target range of sorafenib for thyroid cancer or RCC is not clear.

6. LENVATINIB

6.1. Dosage and Administration Lenvatinib is an oral multi-kinase inhibitor targeting VEGFR 1–3, fibroblast growth factor receptors 1–4, PDGFR-α, rearranged during transfection, and stem cell factor receptor. Lenvatinib is approved for the treatment of radioiodine-refractory differentiated thyroid cancer and advanced and/or metastatic HCC.[77,78] The initial approval dose for thyroid cancer was 24 mg/d. The currently approved starting dosage for HCC is 12 mg/d for body weight ≥60 kg or 8 mg/d for body weight <60 kg. Based on the results of the Phase I study in solid tumors,[79,80] a dose of 24 mg once daily was recommended for thyroid cancer. In contrast, for HCC, dose-finding studies demonstrated that the initial dose was set and was subsequently approved at a lower level, since the impaired hepatic function in patients with HCC may affect lenvatinib exposure.[78,81]

It is difficult for medical oncologists to determine the optimal lenvatinib dosage for each patient. For thyroid cancer, the initial dose of lenvatinib is 24 mg daily; however, a mean lenvatinib dose after adjustment due to severe toxicity was 17.2 mg daily in a phase III study.[77] For HCC, a phase II PK study and simulated population PK study showed that 12 mg was an overdose for patients weighing <60 kg.[82,83] Therefore, the dose for HCC is set and approved based on body weight (12 mg/d for body weight ≥60 kg or 8 mg/d for body weight <60 kg). Despite this dose setting for HCC, lenvatinib frequently induces early and severe toxicities such as fatigue, hypertension, proteinuria, and anorexia, resulting in empiric dose reduction or discontinuation. The incidences of dose reduction and dose interruption due to severe toxicities were 37% and 40%, respectively, in lenvatinib-treated patients in a pivotal phase III trial for HCC.[78] Therefore, predictive markers for toxicity other than body weight are required for HCC. Additionally, a predictive marker for dose adjustment is required for thyroid cancer and HCC.

6.2. Pharmacokinetic Characteristics Lenvatinib is primarily metabolized by CYP3A4 and excreted in the feces. Renal excretion of lenvatinib is very low (< 2.5%). Food

intake did not affect exposure to lenvatinib.[79] Lenvatinib is rapidly absorbed with t_{max} at 1–4 h after administration.[84] The terminal half-life of lenvatinib is 28 h.[85] The apparent oral clearance (CL/F) of lenvatinib is 4.2–7.1 L/h.[85] Protein binding ranged from 96.6% to 98.2%.[80] Renal function had no significant effect on lenvatinib CL/F.[85] pH-elevating agents had no influence on the absorption process of lenvatinib.[85]

6.3. Exposure-Efficacy/Toxicity Relationship Several studies have evaluated a relationship between lenvatinib exposure and dose-limiting toxicities. A previous report showed that the median trough lenvatinib concentration was 62.4 ng/mL on day 15 of cycle 1 in patients administered lenvatinib 12 mg daily for HCC and required dose modifications within 30 d.[82] Our exposure-toxicity analysis showed that the mean trough lenvatinib concentration was significantly higher in the group with grade ≥3 toxicity ($n = 15$) than in the group with grade ≤2 toxicity ($n = 13$).[86] Based on the ROC curve, the threshold value of the trough lenvatinib concentration for predicting grade ≥3 toxicities was 71.4 ng/mL (*AUC*, 0.86; 95% CI, 0.71–1.00; $p < 0.05$). Our result suggests that a lenvatinib trough concentration of ≥71.4 ng/mL is as a threshold for grade ≥3 toxicity of lenvatinib in patients with HCC. From these findings, lenvatinib over-exposure is highly linked to dose-limiting toxicities.

Two published studies have shown that efficacy is related to lenvatinib exposure in HCC. Hata *et al.*[87] reported that maintaining a median trough concentration above 42.68 ng/mL of lenvatinib was crucial for achieving the objective response (CR or PR) rate in HCC patients. Additionally, we showed that the threshold value of the trough lenvatinib concentration associated with disease control status (CR, PR, or SD at best response) for HCC was 36.8 ng/mL.[86] Furthermore, our data showed that patients with HCC exhibiting serum lenvatinib concentrations of 36.8–71.4 ng/mL tended to exhibit prolonged TTF and PFS, and lenvatinib was well tolerated in these patients. Based on the evidence for an exposure-efficacy/safety relationship, optimal lenvatinib range for HCC may be 40–70 ng/mL. In a recent PK/PD analysis in patients with advanced thyroid cancer, the target trough concentration for lenvatinib as the threshold for predicting optimal response was found to be in the range of 42–88 ng/mL.[88]

6.4. Target Concentration We have summarized the guidance of TDM for lenvatinib (Table 1). Lenvatinib PK was assessed using the serum or plasma trough concentration of lenvatinib. We propose that the lenvatinib trough concentration should be monitored from day 8 at a steady state, targeting 40–70 ng/mL for HCC, and 42–88 ng/mL for thyroid cancer. However, PK-guided study of lenvatinib has not been reported yet, and therefore, the cut-off values should be validated in further large prospective studies.

7. PERSPECTIVES

TDM is a useful tool for dose adjustment, but there is little information on the best indicators for individualization of the starting dose. Differences in drug exposure among patients have been shown to be associated with genetic polymorphisms in factors related to pharmacokinetics (for example, drug-metabolizing enzymes and drug transporters). Therefore, the detection of pharmacogenomic (PGx) factors determining the PK of oral multi-kinase inhibitors could predict high blood levels prior to the start of treatment. Among these factors, genetic polymorphisms of the breast cancer resistance protein (BCRP/ABCG2), the efflux transporter, have been reported to have a major impact on exposure to certain oral multi-kinase inhibitors.[2,30,89–91] We hope that further PK/PGx studies will contribute to the precise individualized dosing of oral multi-targeted therapy.

Recently, immuno-oncology has provided a breakthrough in cancer chemotherapy. In this approach, regimens combining immune checkpoint inhibitors with a multi-targeted anticancer agent have shown clinical benefits for advanced carcinoma.[92–94] Additionally, immune checkpoint inhibitors-based therapies have been approved as first-line therapy for various types of cancer, and oral multi-kinase inhibitors are now used as second-line or later therapy after immune checkpoint inhibitors. Immune checkpoint inhibitors have been reported to have long-lasting effects,[95] and may additively or synergistically enhance the clinical efficacy of molecular-targeted therapy. At the same time, new safety concerns have been raised by several studies on molecular-targeted therapy following immune checkpoint inhibitor use.[96–100] However, to date, there have been no reports on the PK interactions between immune checkpoint inhibitors and multi-kinase inhibitors. Therapeutic monoclonal antibodies are not thought to interact directly with CYP enzymes.[101,102] In contrast, cytokines produced by activated T cells can affect the regulation of several drug transporters and CYP enzyme levels; therefore,

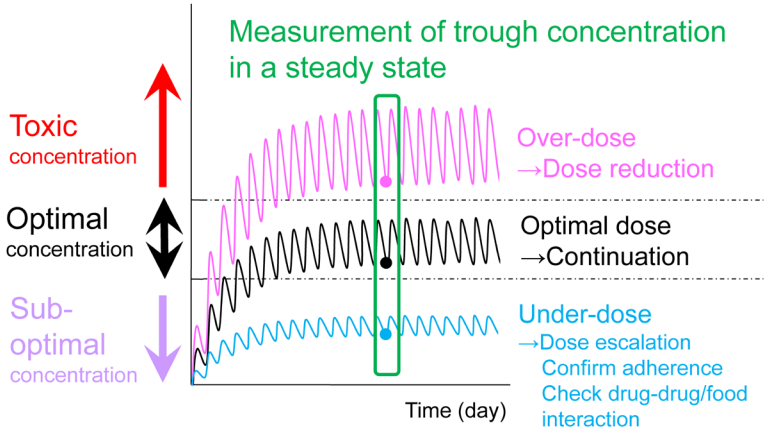

Fig. 1. Dose Optimization of Oral Multi-Kinase Inhibitors Using Therapeutic Drug Monitoring

immunomodulatory antibodies may indirectly affect exposure to small molecule drugs. In the future, this hypothesis should be confirmed in further PK clinical trials.

8. CONCLUSION

In conclusion, dose individualization can be used to achieve optimal drug exposure and best clinical outcomes. The identification of optimal blood ranges would help individualize treatment using oral multi-kinase inhibitors, suggesting that TDM could be useful for dose adjustment of these drugs (Fig. 1).

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Conflict of Interest The authors declare no conflict of interest.

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