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Possibility for dose optimization of pazopanib from its plasma concentration in Japanese patients with cancer

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The currently approved dose of pazopanib (800 mg) is being re-examined owing to its adverse effects. The aim of this study was to evaluate the relationships among starting or maintenance doses of pazopanib, estimated pazopanib $C_{\text{min}}$, and other clinical factors, including albumin and $\alpha$-1 acid glycoprotein levels, in soft-tissue sarcoma and renal cell carcinoma. We also determined whether therapeutic drug monitoring of pazopanib concentrations may be used to improve its therapeutic efficacy and prevent adverse effects. Forty patients who received pazopanib for renal cancer or soft-tissue sarcoma at the Hokkaido Cancer Center were evaluated prospectively. $C_{\text{min}}$ for pazopanib was calculated based on the measured values from the plasma samples. The efficacy and time to treatment failure were then assessed. The pazopanib maintenance doses were 200 mg ($n = 4$), 400 mg ($n = 34$), 600 mg ($n = 4$), and 800 mg ($n = 1$). Most patients (65%) who received a 400 mg dose had an effective pazopanib concentration ($\geq 20 \, \mu g/mL$), whereas 35% of patients who received the 400 mg dose had ineffective concentrations ($< 20 \, \mu g/mL$). Logistic regression analysis revealed that only the albumin level was significantly associated with effective pazopanib concentrations (odds ratio: 1.37, $p = 0.0234$). In conclusion, a dose of 400 mg had been effective and well tolerated in more than half of patients in this study. However, therapeutic drug monitoring is necessary during pazopanib therapy.
Keywords: pazopanib, low dose, albumin, therapeutic drug monitoring
Introduction

Pazopanib (Votrient®, Novartis) is an angiogenesis inhibitor that targets the tyrosine kinases of vascular endothelial growth factor receptors, platelet-derived growth factor receptors, and c-Kit. Oral treatment using pazopanib monotherapy (800 mg/day) is effective for multiple tumor types and is approved for the treatment of advanced renal cell carcinoma and sarcoma.¹⁻⁴) A phase 1 trial of pazopanib was terminated, and the maximum tolerated dose was not achieved as a plateau in steady-state exposure was observed at doses of ≥800 mg/day.⁵) Therefore, despite large interpatient variability in the pharmacokinetics of pazopanib, it was approved at a fixed oral dose of 800 mg/day. However, this dose is associated with various adverse events, including fatigue (65%), diarrhea (58%), nausea (54%), weight loss (48%), hypertension (41%), and loss of appetite (40%). Therefore, the starting doses of pazopanib are being increasingly lowered in an effort to maintain the patient’s quality of life.

In preclinical studies in mouse models, optimal inhibition of tumor angiogenesis was observed when the plasma pazopanib concentrations were maintained at 17.5 µg/mL (40 µmol/L) over the entire dosing period.²) A pharmacokinetic target in the same concentration range has also been identified in clinical studies. For instance, in a phase I study (63 patients with solid tumors),⁵) Hurwitz et al. found that patients with $C_{\text{trough}} >15$ µg/mL had a markedly higher incidence of hypertension than those with lower $C_{\text{trough}}$ values (77% vs. 39%), and that
achieving a $C_{\text{trough}}$ of $>15 \, \mu\text{g/mL}$ appeared to be correlated with clinical activity. Furthermore, in a phase II study (pharmacokinetic data from 205 patients with solid and renal cell carcinomas), Suttle et al. analyzed data from a phase I study that compared patients with $C_{\text{trough}}$ levels of $<20.5 \, \mu\text{g/mL}$ with those having levels of $>20.5 \, \mu\text{g/mL}$; at week 4, the latter had a significantly longer progression-free survival (49.4 weeks vs. 20.3 weeks, $p < 0.005$), higher response rate (45% vs. 18%, $p < 0.0002$), and more extensive tumor shrinkage. In addition, they reported a correlation between $C_{\text{trough}}$ levels and adverse events. However, in clinical cases, the relation between dose, particularly at 400 mg, and the concentration of pazopanib is not well-defined.

Therefore, the present study examined whether the starting dose of pazopanib affected time to treatment failure (TTF), and whether a 400 mg maintenance dose may provide therapeutically effective plasma concentrations without unacceptable adverse events.

**Methods**

**Patients**

This prospective observational study evaluated samples from outpatients who were $>18$ years of age, and had received pazopanib therapy between October 2012 and January 2017 at the National Hospital Organization Hokkaido Cancer Center in Japan. Demographic and clinical data were collected from the start of pazopanib therapy to the end of treatment, and
patients who did not undergo evaluation of pazopanib levels were excluded. Each sample was assayed for α1-acid glycoprotein (A1AG) using the N-assay TIA α1-AG NITTOBO (Nittobo Medical Co. Ltd., Tokyo, Japan). TTF was defined as the period from the first day of pazopanib therapy to the day of cessation owing to any cause (including disease progression or adverse events). In this study, the dose that was continued for over 30 days was defined as the maintenance dose.

All procedures involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

The study protocol was approved by the National Hospital Organization Hokkaido Cancer Center Human Research Ethics Committee (29-18).

**Pharmacokinetics**

All pazopanib concentration data were obtained using ultra high-performance liquid chromatography (UHPLC) analysis, with sample preparation; the UHPLC measurements were performed as previously described with minor modifications. The patients’ medical records were individually reviewed using a standardized data collection template at the study site, in order to obtain their demographic and clinical data (i.e., treatment outcomes, adverse
events, pazopanib dosing information, and concomitant medications taken during pazopanib therapy). The estimated $C_{\text{min}}$ values were determined using methods described by Verheijen et al.\textsuperscript{9)}: samples were drawn at routinely scheduled visits to the outpatient clinic. All plasma samples were collected after medical examinations. The date and time of the last intake of the pazopanib dose, and the time of plasma sampling were recorded. $C_{\text{min}}$ values were calculated based on the measured concentrations and intervals between last ingested doses and sample times using the algorithm developed previously for imatinib and pazopanib.\textsuperscript{9, 10)} Samples drawn before $T_{\text{max}}$ (2 h), \textsuperscript{5)} or more than 24 h after the last dose were excluded from the analysis. The estimated $C_{\text{min}}$ was calculated for each patient based on the one-compartment model, which was based on the elimination rate constant ($K_e$) from the evaluation form, and the time from the drawing of blood to the next treatment. The $K_e$ was calculated using the mean half-life of pazopanib, that is 30.9 h\textsuperscript{9)}.

Statistical analysis

All analyses were performed using GraphPad Prism (version 5.0) and EZR software. Continuous and categorical variables were compared using the Mann-Whitney U and Fisher’s exact tests, respectively. Treatment lengths included the period from the start to the end of pazopanib administration, and were evaluated using Kaplan-Meier curves and the log rank test; binary logistic regression analysis was performed, and P values $<$0.05 were considered
Results

A total of 73 patients were included in the starting dose analysis between October 2012 and January 2017; among them, 33 had renal cell carcinoma and 40 had soft tissue sarcoma. Figure 1 illustrates the relationship between the starting dose and TTF of pazopanib therapy.

The starting doses of pazopanib (once daily) were 400 mg (31 cases), 600 mg (31 cases), and 800 mg (11 cases). The median treatment durations were 112 days for the 400 mg dose, 25 days for the 600 mg dose, and 14 days for the 800 mg dose ($P = 0.00174$). The patient demographic and clinical characteristics are shown in Table 1. Overall, 9 of 11 (82%) patients experienced adverse events (AE) include diarrhea, fatigue, and liver injury; 2 of 11 (18%) were in the progressive disease (PD) phase. These adverse events led to discontinuation with the starting dose of 800 mg. In cases administered the 600 mg dose, AEs and PD were observed in 21 of 31 (68%) and 9 of 31 (29%) patients, respectively. Moreover, 4 of 31 (13%) patients experienced AEs including fatigue; 27 of 31 (87%) experienced PD with the 400 mg dose. The performance status and the number of regimens before pazopanib therapy were compared; however, a clear difference was not observed (Table 2).

Plasma samples were obtained from a total of 47 participants for calculating the $C_{\text{min}}$ of pazopanib (Fig. 2). During sampling, 85% received half of the standard dose (400 mg),
although $C_{\text{min}}$ was frequently $>20$ $\mu$g/mL (Fig. 2). In the 400 mg group, the $C_{\text{min}}$ and the patient body surface areas did not appear to be correlated (data not shown). As shown in Fig. 3, the median TTF in those receiving a daily dose of 400 mg with $C_{\text{min}} \geq 20$ $\mu$g/mL and $<20$ $\mu$g/mL was 352 and 210 days, respectively ($p = 0.434$). In the group with pazopanib levels $\geq 20$ $\mu$g/mL, 3 of 29 (10.3%) patients experienced grade 1 fatigue and/or diarrhea during treatment. However, in the group with levels $<20$ $\mu$g/mL, 3 of 14 (21%) patients experienced grade 1 toxicities including fatigue or diarrhea. Only 1 patient in both groups had grade 2 diarrhea ($C_{\text{min}}= 28.7$ $\mu$g/mL).

**Factors affecting estimated pazopanib $C_{\text{min}}$**

Table 3 shows the results of the analysis in the groups receiving the 400 mg maintenance dose, with pazopanib levels above or below the effective cut-off concentration ($C_{\text{min}}$ of $<20$ $\mu$g/mL or $\geq 20$ $\mu$g/mL). As shown in table 3, higher pazopanib concentrations were significantly associated with patient age, cancer type, and human serum albumin (Alb) levels on the day of pazopanib sampling (all $P < 0.05$). The pazopanib concentrations were not significantly associated with body surface area, pazopanib dose, or alpha-1 acid glycoprotein (A1AG) levels. Logistic regression analysis revealed that the Alb level was independently associated with a significant change in pazopanib concentrations (Table 4). Pazopanib $C_{\text{min}}$ was not significantly affected by any of the concomitant drugs, which included calcium channel blockers, furosemide, histamine 2 receptor antagonists, proton pump inhibitors, and
angiotensin 2 receptor blockers. In this study, the effect on pazopanib concentrations could not be evaluated as the number of patients taking proton pump inhibitors was limited.

**Discussion**

Overall, 82 % (9 of 11) patients in this study experienced adverse events with pazopanib, and could not continue using this medication at the standard dose of 800 mg/day. In the present study, the TTF was prolonged with the 400 mg dose, which is half the standard starting dose (Fig. 1).

Moreover, among patients who received the 400 mg dose, 65% achieved a $C_{min}$ of $>20 \mu g/mL$ (Fig 2); this indicates that sufficient therapeutic effect may be achieved using a lower dose. Furthermore, used in conjunction with therapeutic drug monitoring, a dose of 400 mg may allow prolonged treatment and may be well tolerated by patients, with fewer dose reductions or treatment discontinuations related to adverse events (Fig. 1, Fig. 3). Although not significant, the plasma pazopanib concentrations of $\geq 20 \mu g/mL$ appeared to improve efficacy, even with a dose of 400 mg. In this study, the sample size was small and because of this, our results did not reach statistical significance in the Kaplan–Meier analysis (Fig. 3). Additionally, the difference in efficacy from that of previous studies may be attributed to the inclusion of selected patient groups categorized by cancer type, stage, and/or clinical practice. Further intervention studies are needed to validate our findings. However, 35% of patients in
this study who received a maintenance dose of 400 mg did not achieve effective concentrations of pazopanib.

The inter-patient variability in the pharmacokinetics of pazopanib may not be exclusively related to Alb, as the absorption process of the drug may also lead to variability. In this context, pazopanib is soluble in aqueous media at a pH of 1, and is practically insoluble at a pH of >4; this indicates that the stomach acid and contents may affect pazopanib absorption.13) Furthermore, pazopanib is a class II drug according to the biopharmaceutics classification system, with high permeability and low solubility; most of the orally taken pazopanib is eliminated in the feces, unabsorbed; this is consistent with the limited solubility of the orally administered drug. The mean absolute bioavailability from a once daily oral dose of 800 mg was determined to be 21.4% (range: 13.5–38.9%), by comparing the area under the concentration-time curve dose-normalized ratio during a 24 h day, and the AUC from time 0 to ∞ for a 5 mg intravenous dose.12, 13)

Pazopanib is primarily metabolized by CYP3A4, and to a lesser extent by CYP1A2,13, 14) however, the precise underlying mechanisms are unclear. It is also unclear whether the concentrations of pazopanib decrease owing to the autoinduction of CYP3A4, and the effects of inter-patient variability remains a complex area. A dose of 800 mg/day was selected for phase II and phase III clinical trials based on target plasma C_{trough} values that were associated with clinical and biological effects in preclinical models and in patients with solid tumors.1, 3)
However, inter-patient heterogeneity in the metabolism and/or absorption of pazopanib may lead to differences in systemic exposure. Therefore, although pharmacokinetic parameters influence toxicity and efficacy, only a few of many possible factors need to be controlled during drug dose optimization; this may also include other important factors (e.g., toxicity as a marker of efficacy rather than a limiting factor for titration, blood- or tissue-based biomarkers, and imaging).

Unfortunately, the present study used a therapeutic drug algorithm validated for imatinib, that was calculated from the mean half-life to $C_{\text{min}}$; therefore, we could not examine individual-level differences in excretion owing to the out-patient status of the participants. However, this algorithm describes a general exponential decline in exposure with a specified plasma half-life; it would therefore also be suitable for pazopanib. The liver is the main organ for excretion of pazopanib. Reports comparing the pharmacokinetics among patients with liver dysfunction have reported that the clearance is similar, except for those with severe liver injury.\textsuperscript{15) This study did not include patients with moderate or severe liver dysfunction.

In addition, the estimated pazopanib concentration in this cohort was modestly correlated with the Alb levels ($r^2 = 0.371$); however, as we had evaluated the total plasma samples in the present study, the contributions of Alb and A1AG were difficult to estimate. This may be attributed to the fact that most patients in the two groups had a clinically normal range of albumin. Since the results indicate that the impact of albumin levels on the pharmacokinetics...
of pazopanib is minimal.

The present study revealed that a high proportion of patients who received an initial dose of 400 mg (one-half of the standard dose) had effective plasma concentrations of pazopanib. Furthermore, the correlation between the estimated pazopanib concentrations and Alb was slightly higher than that with A1AG; in addition, the Alb levels independently influenced $C_{\text{min}}$ on logistic-regression analysis (odds ratio: 1.37, $P = 0.0234$). Therefore, monitoring of the therapeutic plasma concentrations is necessary for adequate dose adjustment during pazopanib therapy. This may aid in personalizing and optimizing treatment outcomes. Further studies on larger and more diverse cohorts are needed to validate our findings.

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**Conflict of Interest**

The authors declare no conflict of interest.
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Table 1. The demographic characteristics of the cohort

|                        | Patient       |
|------------------------|---------------|
| Sex (M/F)              | 73 (38/35)    |
| Age (median years)     | 55.1 (18–84)  |
| Cancer type            |               |
| Soft tissue            | 40            |
| Renal cell             | 33            |
| Weight (kg)            | 54 ± 7.8      |
| Height (cm)            | 159 ± 7.8     |
| BSA (m²)               | 1.5 ± 0.2     |

M: male; F: female; BSA: body surface area
Table 2. Comparison between groups based on starting dose of pazopanib therapy

| Pazopanib dose | 800 mg | 600 mg | 400 mg |
|---------------|--------|--------|--------|
| Performance Status |
| 0             | 6      | 22     | 16     |
| 1             | 4      | 6      | 14     |
| 2             | 1      | 3      | 1      |
| The number of regimens before pazopanib therapy |
| 0             | 2      | 11     | 5      |
| 1             | 2      | 5      | 11     |
| 2             | 6      | 13     | 13     |
| 3             | 1      | 1      | 1      |
| 5             | 0      | 1      | 1      |
Table 3. Comparison between groups receiving the 400 mg maintenance dose with pazopanib concentrations above or below the effective cut-off concentration (20 µg/mL)

| Paz conc.                        | < 20 µg/mL | ≥20 µg/mL | p-value |
|----------------------------------|------------|-----------|---------|
| Sex (M/F)                        | 14 (6/8 )  | 26 (9/17 )| 0.736a  |
| Age (median years)               | 65 (48–78 )| 52 (22–76 )| 0.048²b |
| Cancer type                      |            |           | 0.030¹a  |
| Soft-tissue sarcoma              | 1          | 11        |         |
| Renal cell                       | 13         | 15        |         |
| Weight (kg)                      | 51 ± 12    | 56 ± 12   | 0.133b  |
| Height (cm)                      | 159 ± 9.7  | 159 ± 6.8 | 0.733b  |
| BSA (m²)                         | 1.5 ± 0.2  | 1.6 ± 0.2 | 0.183b  |
| Dose (mg)                        | 400 ± 36   | 415 ± 19  | 0.404b  |
| The days from a start to plasma sampling| 203 ± 44  | 352 ± 55  | 0.0695b |
| BUN (mg/dL)                      | 17 ± 1.8   | 14 ± 1.1  | 0.0915b |
| Scr (mg/dL)                      | 0.91 ± 0.11| 0.75 ± 0.049| 0.419b |
| Alb (mg/dL)                      | 3.3 ± 0.17 | 3.9 ± 0.087| 0.0048b |
| A1AG (mg/dL)                     | 132 ± 22   | 126 ± 11  | 0.571b  |
| AST (mg/dL)                      | 25 ± 3.9   | 23 ± 1.2  | 0.628b  |
| ALT (mg/dL)                      | 17 ± 2.7   | 19 ± 1.7  | 0.485b  |
| T-bil (mg/dL)                    | 0.63 ± 0.070| 0.77 ± 0.074| 0.202b |
| Ca channel blocker               | 11         | 20        | 1.00⁰a  |
| Furosemide                       | 2          | 5         | 0.690a  |
| H2 receptor antagonist           | 9          | 9         | 0.101a  |
| Proton pump inhibitor            | 6          | 1         | 1.00⁰a  |
| Angiotensin II receptor blocker  | 6          | 7         | 0.480⁰a |

¹ Fisher exact test; ² Mann-Whitney u test;

BSA: body surface area; BUN: blood urea nitrogen; Scr: serum creatinine; Alb: human serum albumin; A1AG: α1-acid glycoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; T-bil: total bilirubin
Table 4. Logistic regression analysis of the categories obtained from Table 2.

|                          | Odds   | 95% CI      | p-value |
|--------------------------|--------|-------------|---------|
| Age (mean years)         | 1.01   | (0.927–1.10)| 0.841   |
| Cancer type              | 0.132  | (0.00714–2.45)| 0.174 |
| Alb (mg/dL)              | 1.25   | (1.26–124)  | **0.031** |

Alb: albumin; CI: confidence interval
Fig 1. Kaplan-Meier curves for the duration of pazopanib treatment according to the starting dose.

Curves for 400 mg (n = 31, solid line), 600 mg (n = 31, semi-dashed line), and 800 mg (n = 11, dashed line).

The median TTFs were 112 days for the 400 mg dose, 25 days for the 600 mg dose, and 14 days for the 800 mg dose (P = 0.00174).

TTF: time to treatment failure
Fig 2. Relationship between estimated pazopanib $C_{\text{min}}$ and dose.
Fig 3. Kaplan-Meier curves for the duration of pazopanib treatment with a 400 mg maintenance dose according to estimated pazopanib $C_{\text{min}}$. $C_{\text{min}} \geq 20 \ \mu\text{g/mL}$ (n = 26, solid line), < 20 \ \mu\text{g/mL}$ (n = 14, dashed line). The median TTF was 352 days for concentrations $\geq 20 \ \mu\text{g/mL}$, and 210 days for concentrations < 20 \ \mu\text{g/mL}$ (P = 0.434).

TTF: time to treatment failure