Review Article

Drug review: Pazopanib

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Abstract

Pazopanib (Votrient®) is an oral small-molecule multi-kinase inhibitor that primarily inhibits vascular endothelial growth factor receptor-1, -2 and -3, platelet endothelial growth factor receptor-α, and -β, and the stem-cell factor receptor c-kit. In preliminary experiments using angiogenesis models with mice and rabbits, pazopanib inhibited angiogenesis caused by combined vascular endothelial growth factor and basic fibroblast growth factor. Although pazopanib was developed as a therapeutic agent against various tumors, it is currently approved in many countries for advanced soft-tissue sarcoma and renal cell carcinoma. The importance of pazopanib has been acknowledged, with positive results demonstrated in large-scale clinical trials involving patients with soft-tissue sarcoma and renal cell carcinoma. However, adverse events such as liver dysfunction and hypertension are common, often necessitating treatment discontinuation. These adverse events are generally manageable, and from the perspective of health-related quality of life and cost-effectiveness, pazopanib provides an improvement in quality-adjusted life years and decreases the treatment cost compared with other alternatives. In this review, we present the results of clinical trials and discuss the pharmacological action of pazopanib, with the aim of evaluating its current state by examining various associated issues.

Key words: pazopanib, soft tissue sarcoma, renal cell carcinoma

Introduction

Pazopanib, developed by GlaxoSmithKline and now patented by Novartis, is an oral multi-kinase inhibitor that blocks vascular endothelial growth factor receptor (VEGFR)-1, -2 and -3, platelet endothelial growth factor receptor (PDGFR)-α, and -β, interleukin-2 receptor-inducible T-cell kinase (ITK), leukocyte-specific protein tyrosine kinase (LCK), colony-stimulating factor-1 receptor (c-fms), fibroblast growth factor receptors (FGFR-1 and -3), and the stem cell factor receptor c-kit (Fig. 1) (1). Although pazopanib was developed as a therapeutic agent for various types of cancers, it is currently only approved for the treatment of advanced soft-tissue sarcoma (STS) and renal cell carcinoma (RCC).

Soft tissues include the skeletal muscle, smooth muscle, adipose tissue, fibrous tissue, blood vessels developed from the mesoderm, and peripheral nerve tissue developed from the neuroectoderm. Thus, a soft-tissue tumor is defined as a tumor that develops or differentiates from above-mentioned tissues. Because there are over 50 tissue subtypes, and some are extremely rare, tumor diagnosis can be difficult. Currently, the World Health Organization (WHO) classification is widely used for classifying tissue types (2). Moreover, the incidence rate of STS is low, and was reported to be ~6% in children and 1% in adults among all malignant tumors (3). The lung is the most common site of metastasis in patients with STS and the median survival period is 8–12 months; therefore, the prognosis is poor (4). Although there are diverse tissue types in STS, many cases exhibit the overexpression of VEGF and PDGF (5,6), and a correlation between its grade of malignancy and survival has been reported (7,8). This background information supports the validity of treatment that targets kinases, such as VEGFR and PDGFR.

Clear cell carcinoma that constitutes the majority of RCC cases is often associated with the loss of von Hippel Lindau (VHL) protein.
functionality along with a mutation in the VHL gene (9). As a result, hypoxia-inducible factor (HIF) accumulates, and under normal oxygen concentrations, the expression of gene triggered under hypoxia (e.g., erythropoietin) is enhanced. Under hypoxia, angiogenesis is promoted to supply more oxygen to the soft tissues via the production of vascular endothelial growth factor (VEGF). With RCC, VEGF production is constantly increased. Thus, by inhibiting VEGF signaling, tumor-induced angiogenesis is inhibited and, thereby inhibiting tumor growth. This is the main mechanism by which angiogenesis inhibitors act against RCC (9). Furthermore, decreased PTEN and HIF levels are known to stimulate the PI3K/Akt/mammalian target of the rapamycin (mTOR) pathway in cases of RCC; therefore, controlling this pathway using mTOR inhibitors can produce antitumor effects, thereby inhibiting angiogenesis and cell proliferation (10,11). Previously, interferon (IFN)-α or interleukin (IL)-2 were widely used to treat RCC; however, standard chemotherapy has changed to involve molecular targeted or immuno-oncology (I-O) therapies. In Japan, angiogenesis inhibitors (e.g., sorafenib, sunitinib, axitinib and pazopanib), mTOR inhibitors (e.g., everolimus and temsirolimus), and I-O drugs (e.g., nivolumab) have been approved for RCC.

In this review, we will present the pharmacological action of pazopanib and clinical trial results, and re-evaluate its importance for the treatment of STS and RCC.

Pharmacological mechanism

Pazopanib is a multi-tyrosine kinase inhibitor that competes with adenosine triphosphate for binding to the intracellular side of tyrosine kinase receptors and prevents the ATP-induced activation of these receptors. Regarding its phosphorylation-inhibitory action, pazopanib is an inhibitor of the kinases VEGFR-1, -2 and -3, PDGFR-α, and -β, c-Kit, FGFR-1, and -3 with an IC50 of 10, 30, 47, 71, 84, 74, and 140 nM, respectively (12). In a murine in vivo experiment, the inhibitory activity against VEGFR-2 phosphorylation was confirmed when the plasma concentration of pazopanib was ≥17.5 μg/ml (1). In an in vitro study, pazopanib did not demonstrate direct cytostatic activity against most STS cell lines. However, it inhibited human umbilical vein endothelial cells (HUVEC) stimulated by VEGF or basic fibroblast growth factor (bFGF) (1). It also inhibited angiogenesis in a murine laser-induced choroidal neovascularization model and a hydron pellet model containing rabbit VEGF/bFGF (12). According to these experiments, pazopanib blocks VEGF, FGFR and PDGFR signaling associated with angiogenesis. In addition, it mediates its anti-tumor effect by an angiogenesis-inhibitory action, which prevents the formation of new tumor vessels. On the other hand, because the concentration at which the growth of some STS cells (human rhabdomyosarcoma A 204 cell line, human synovial sarcoma SYO-1 cell line, and human synovial sarcoma HS-SY-II cell line) was inhibited was only ~1/20 of the plasma trough concentration of the recommended clinical dose administered to humans, pazopanib might exert its anti-tumor effect through direct tumor-growth inhibition independent of its angiogenesis-inhibitory action (13).

Phase I trials

A Phase I clinical trial (VEG100003 study) of pazopanib monotherapy conducted on solid cancer patients examined multiple doses and regimens (50–2000 mg once a day, 300 or 400 mg twice a day, or 50 or 100 mg three times a week). The results revealed that the pazopanib concentration in blood peaked at 2–4 h after the ingestion 800 mg, with a half-life of 30.9 h. The area under the curve (AUC) was 743.3 μg/ml and the maximum drug concentration (Cmax) was 45.1 μg/ml. An oral dose greater than 800 mg (800–2000 mg/day) did not show an increase in the AUC and Cmax of pazopanib, indicating it reached a plateau. Therefore, the administration of 800 mg pazopanib once a day was selected as the dose and regimen for a Phase II clinical trial (14). In particular, of six cases that exhibited a partial response (PR) or stable disease (SD) RCC according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, five cases (83%) had a plasma pazopanib concentration of ≥15 μg/ml 24 h after the administration on Day 22 at a steady state (C24). However, C24 was <15 μg/ml at a steady-state for all four progressive disease (PD) RCC cases. Moreover, the C24 was ≥15 μg/ml for 93% of patients who were taking 800 mg pazopanib once a day.

In a Phase I clinical trial conducted in Japanese solid cancer patients, repeated administration of pazopanib was examined in part A, in which a single administration of one of the three doses (400, 800 or 1000 mg) was delivered on the first day and one of the two doses (800 or 1000 mg once a day) on the second day or later (15). The results revealed the tolerability of Japanese patients to the oral administration of 800 mg or 1000 mg pazopanib once a day. In addition, on Day 22 the geometric mean of C24 for the oral administration of 800 mg pazopanib once a day was >15 μg/ml, which indicates a clinical effect. Therefore, the oral administration of 800 mg pazopanib once a day was confirmed to be an appropriate dose for Japanese patients. In part B, the combined used of pazopanib with lapatinib was examined; one RCC patient showed no disease advancement for 17 months (16). Because the pharmacokinetic behavior of children may differ from that of adults, a Phase I trial was conducted on children and youths aged between 2 and 21 years old with a recurrent solid tumor or primary central nervous system lymphoma to determine the maximum-tolerated dose (MTD) for the two dosage forms of tablets and syrup so as to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of pazopanib according to the dosage form (17). Because high bioavailability was reported for syrup compared with tablets in adults, this trial commenced with a low dose of syrup. In two out of four cases, dose-limiting toxicity (DLT) because of increased alanine aminotransferase (ALT) was confirmed at a low dose of 225 mg/m². Ultimately, MTD was indicated at 450 mg/m².
for the tablets and 160 mg/m² for the syrup. The maximum concentration in the blood of children who received the tablets (450 mg/m²) was 21.5 μg/ml, which was equivalent to the 800 mg dose for adults. A total of 51 cases with various tumors (e.g., sarcoma and brain tumors) were analyzed, and tolerability to pazopanib was shown for children. Two patients achieved PR; eight patients showed SD of ≥6 months, seven of whom had sarcoma. In this trial, there was no clear difference in the pharmacokinetic parameters between the tablets and syrup; however, this might be due to the small number of subjects and differences in individual PKs.

The National Cancer Institute Organ Dysfunction Working Group (NCI ODWG) conducted a Phase I trial of pazopanib on patients with liver dysfunction (18). In 98 registered cases, the MTD of the mild liver dysfunction group (bilirubin was within the normal range but ALT exceeded the upper limit of the normal range, or regardless of ALT, bilirubin was 1.5 times the upper limit of the normal range) was 800 mg/day, whereas it was 200 mg/day for the moderate group (regardless of ALT, bilirubin was 1.5–3 times the upper limit of the normal range) and the severe group (regardless of ALT, bilirubin was ≥3 times the upper limit of the normal range). However, the PK did not exhibit any difference based on the degree of liver dysfunction. Compared with patients with no liver dysfunction receiving a dose of 800 mg/day, the AUC of the moderate group and severe group receiving a dose of 200 mg/day were only 39% and 15%, respectively. These results led to a recommendation of 200 mg/day for the starting dose for patients with moderate liver dysfunction; however, it should be noted that the concentration in the blood may not have reached therapeutic levels.

### Table 1. Inhibiting action of pazopanib against purified kinases (1)

<table>
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<th>Enzyme</th>
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### Pazopanib for soft tissue sarcoma

The European Organization for Research and Treatment of Cancer (EORTC) conducted a Phase II trial (EORTC 62043 study) to examine the efficacy and safety of pazopanib (Table 2) (19). In this trial, the progression-free rate (PFR) at 12 weeks was the primary endpoint, and efficacy and safety were evaluated when 800 mg of pazopanib was administered orally once a day to 142 patients with high-grade or intermediated-grade advanced STS who had a previous history of chemotherapy or were ineligible for chemotherapy. Regarding efficacy, STS was classified into four groups and evaluated based on the tissue types: (1) leiomyosarcoma, (2) adipocytic sarcoma, (3) synovial sarcoma and (4) other eligible sarcomas.

PFR at 12 weeks was 44% (18/41 cases), 49% (18/37 cases) and 39% (16/41 cases) for leiomyosarcoma, synovial sarcoma and other eligible sarcomas, respectively, confirming the antitumor effect of pazopanib against these STSs. Adipocytic sarcoma was associated with a small number of progression-free patients (3/17 cases) in the interim evaluation according to the facility pathological diagnosis; thus, further enrollment of such cases was discontinued. However, the final PFR according to central pathological diagnosis was 26% (5/19 cases). The median overall PFS was 12.1 weeks (95% CI: 12.0–22.4), whereas the median overall survival (OS) was 10.6 months (95% CI: 9.5–11.7). The median PFS for adipoctytic sarcoma was 11.1 weeks (95% CI: 7.1–11.9), whereas the median OS was 6.5 months (95% CI: 4.2–19.3), which was the worst among the four groups. With regard to the outcomes, there were no cases of a complete response (CR), but nine with PR (one with leiomyosarcoma, five with synovial sarcoma, and three with other eligible sarcomas). Furthermore, there were 14 cases in which pazopanib was successful in disease control for ≥1 year (9.9%), indicating that it may be extremely effective for certain patient groups.

The main side effects included hypertension (40.1%), fatigue (36.6%), hypopigmentation (36.6%), nausea (35.9%) and diarrhea (30.3%). In addition, there was an increase in liver enzymes, myelosuppression and proteinuria, most of which were Grade 1 or 2 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3.0. The main side effects ≥ Grade 3 were hypertension (7.7%), fatigue (7.7%) and hyperbilirubinemia (6.3%). Treatment was interrupted for 60% of the total cases, and 23% required a dose reduction; the incidence of severe side effects was low, demonstrating the tolerability of pazopanib. However, nine cases (6%) were discontinued because of toxicities, including bowel perforation and pulmonary embolism.

To further evaluate the efficacy and safety of pazopanib compared to a placebo as the control, a Phase III clinical trial was conducted (PALETTE study) (Table 2) (21). In this trial, using the PFS as the primary endpoint, the efficacy and safety of 800 mg pazopanib or a placebo administered orally once a day were evaluated in STS patients with metastatic lesions who exhibited progression in response to pre-treatment with an anthracycline-based agent. In this trial, the crossover of exacerbation in the placebo group was not acknowledged.

A total of 369 STS patients (excluding liposarcoma, embryonal rhabdomyosarcoma, chondrosarcoma, osteosarcoma, Ewing tumors, primitive neuroectodermal tumor, gastrointestinal stromal tumor, dermatofibrosarcoma protuberas, inflammatory myofibrolastic sarcoma, malignant mesothelioma and mixed mesodermal tumors of the uterus) were randomly assigned to the pazopanib group (246 cases) or the placebo group (123 cases) at a ratio of 2:1. The median primary endpoint, i.e., PFS, was 4.6 months in the pazopanib group (95% CI: 3.7–4.8) and 1.6 months in the placebo group (95% CI: 0.9–1.8). The hazard ratio was 0.31 (95% CI: 0.24–0.40; P < 0.0001), and the pazopanib group showed a statistically longer PFS than the placebo group. In the Japanese subgroup, the PFS of the pazopanib group (24.7 weeks; 95% CI: 8.6–28.1) was significantly longer than the PFS of the placebo group (7.0 weeks; 95% CI: 4.0–11.7) (HR = 0.41 [95% CI: 0.19–0.90]; P = 0.002) (22). According to univariate Cox analyses, performance status (0 vs. 1), fewer lesions of systemic therapy (0–1 vs. 2–4), and lower tumor grade (1 and II vs. III) were extracted as the prognostic factors; however, in the multivariable model, PS and tumor grade were favorable prognostic factors. Although an interorganizational predictive analysis was performed, there was no significant difference between the groups. The median OS was 12.5 months in the pazopanib group (95% CI: 10.6–14.8) and 10.7 months in the placebo group (95% CI: 8.7–12.8),
## Table 2. Effects of pazopanib on soft tissue sarcoma and adverse events

| Trial or authors | EORTC 62 043 (19) | Samuels et al. (20) | PALETTE (21,22) |
|------------------|-------------------|---------------------|-----------------
|                  | Phase 2           | Phase 2             | Phase 3         |
|                  | Number | PFR at 12 weeks (%) | PFS (week) | OS (month) | PFS (month) | OS (month) | Number | PFS (month) | OS (month) | Number | PFS (week) | OS (month) |
| ALL              | 142    | 41                 | 12.1       | (12.0–22.4) | 10.6       | (9.5–11.7) | 246    | 12.5       | (10.6–14.8) | 31     | 24.7       | (8.6–28.1) |
| LMS              | 42     | 44                 | 17.2       | (12.0–24.1) | 11.7       | (10.6–17.6) | 115    | 4.6        | (3.1–5.3)  | 16.7   | NE         | (7.9–28.8) |
| SYN              | 38     | 49                 | 23.4       | (11.7–29.3) | 10.3       | (7.6–13.2) | 30     | 4.1        | (2.0–6.2)  | 8.7    | 46%        | (5.7–14.6) |
| OTH              | 43     | 39                 | 14.0       | (12.0–36.3) | 9.8        | (7.6–11.3) | 101    | 4.6        | (3.0–6.2)  | 1.03   | NE         | (8.0–13.6) |
| LIP              | 19     | 26                 | 11.1       | (7.1–11.9)  | 6.5        | (4.2–19.3) | 41     | 12.6       | (8.5–12.6) | 16%   | 50%        | (7.9–28.8) |

| Discontinued due to toxicity | 6% | 17.1% | 20% | 16% |
| Hypertension (≥Grade 3)       | 40.1% (7.7%) | 36.6% | 41% (7%) | 52% (16%) |
| Increased AST (≥Grade 3)      | 46.4% (4.2%) | NE | 65% (6%) | 51% (8%) |
| Increased ALT (≥Grade 3)      | 50.0% (4.2%) | NE | 46% (10%) | 52% (16%) |

CI, confidence interval; PFR, progression-free rate; PFS, progression survival; OS, overall survival; LIP, adipocytic sarcoma; LMS, leiomyosarcoma; SYN, synovial sarcoma; OTH, other eligible sarcoma; AST, aspartate aminotransferase; ALT, alanine aminotransferase; NE, not evaluated.
with a hazard ratio of 0.86 (95% CI: 0.67–1.11; \( P = 0.25 \)); thus, there was no statistically significant difference. As the best overall response, 14 of 246 cases in the pazopanib group (6%) exhibited PR, whereas 164 cases (67%) were SD. In the placebo group, there was no PR, whereas 47 of 123 cases (38%) were SD. Major adverse events included fatigue (65% in the pazopanib group and 49% in the placebo group), diarrhea (58% vs. 16%), nausea (54% vs. 28%), weight loss (48% vs. 20%), hypertension (41% vs. 7%) and anorexia (40% vs. 20%). Regarding liver enzyme levels, increases in γ-glutamyltransferase (13% vs. 11%), ALT (10% vs. 3%), aspartate aminotransferase (AST) (8% vs. 2%), and bilirubin in blood (2% vs. 2%) were confirmed. In addition, the left ventricular ejection fraction was reduced in 7% of the cases (n = 16), and eight showed an improvement. Five out of eight cases continued with the administration of pazopanib, but three cases needed discontinuation for other reasons. In this trial, the health-related quality of life (HR-QOL) was also evaluated at 4, 8 and 12 weeks after the start of treatment using the EORTC Quality-of-Life Questionnaire (QLQ-C30) (23). There was no significant difference in global health status between the pazopanib and placebo groups (\( P = 0.291 \)); it tended to decrease in both groups during the course of treatment. By other subscales, the pazopanib group had substantially worse results for diarrhea, loss of appetite, nausea/vomiting and fatigue.

Thus, pazopanib was selected as a new treatment option for advanced STS patients with a history of pretreatment with chemotherapy; however, it should be noted that no clear improvement in HR-QOL was reported because of its toxicity and other factors.

Soft-tissue tumors are diverse mesenchymal tumors with >50 histological subtypes. Because of its diverse nature and low incidence rate, excluding gastrointestinal stromal tumors, there has been no significant progress in its treatment, and doxorubicin and ifosfamide continue to play a central role. For STS that cannot be resected or has led to metastatic recurrence, doxorubicin monotherapy remains the first-line treatment to date (24). The combination therapy of docetaxel and gemcitabine, which is routinely used clinically and has shown positive results in Phase II trials, did not exhibit significantly extended PFS in a Phase III trial compared with doxorubicin monotherapy as the first-line treatment (25). In recent years, the efficacy of new agents as second-line treatments or beyond (e.g., trabectedin, eribulin and pazopanib) has been shown, and the treatment results for patients with STS continue to improve. The results of clinical trials of these agents have led to a focus on the difference in response according to tissue type. Trabectedin and dacarbazine were compared in a Phase III trial involving 518 patients with liposarcoma or leiomyosarcoma, who were treated with anthracycline-based drugs and one or more regimens; a significant extension of PFS was confirmed for trabectedin (26). In particular, the RR for myxoid liposarcoma was 51% in a retrospective analysis (27). Moreover, eribulin was compared with dacarbazine in a Phase III trial of 452 patients with liposarcoma and leiomyosarcoma, and a significant extension in OS was confirmed (28). It was especially effective for the treatment of differentiated liposarcoma and pleomorphic liposarcoma, for which an effective treatment has not been established (29). In addition, pazopanib resulted in a significant extension of PFS compared with placebo in a Phase III trial that excluded cases with liposarcoma that showed insufficient effects in a Phase II trial (EORTC 62 043 study), was excluded. However, preclinical data indicated the tumor-inhibitory activity of pazopanib in liposarcoma xenograft models (30). Therefore, the effects of pazopanib on liposarcoma were prospectively examined. Samuels et al. examined the PFR for pazopanib administration as a primary endpoint with 41 patients with intermediate-grade or high-grade liposarcoma. They reported PR in only one case, but the PFR at 12 weeks was good at 68.3% (95% CI: 51.9–81.9) (20). However, in a Japanese retrospective study, the median PFS of pazopanib for the treatment of 33 liposarcoma cases was extremely poor (8 weeks) (31). Because many previous examinations were small scale studies, there continues to be room for discussion of the effects of pazopanib on liposarcoma. An advantage of pazopanib is its long-term success. In two clinical trials (EORTC 62 043 and PALETTE study), 12 of the total cases (3.5%) maintained clinical usefulness for ≥2 years, and the median duration of pazopanib administration in these cases was 2.4 years (the longest was 3.7 years) (32). Therefore, the existence of super responders for pazopanib is indicated. However, the efficacy of new drugs for each tissue type is unknown and experts still debate the selection of therapeutic agents depending on the pathological tissue types of STS.

Recently, molecular biological analyses have gradually elucidated specific fusion genes and characteristic gene expressions for each pathological tissue type of STS, and there appears to be light at the end of the tunnel for therapeutic development for each pathological tissue type. There are some pathological tissue types of STS for which drugs other than doxorubicin are recommended as the first-line agent according to their molecular characteristics, and these drugs are listed in the guidelines (33). Alveolar soft part sarcoma (ASPS) is an extremely rare STS with onset in young patients, and is generally resistant to doxorubicin (34). Because tumors exhibit a histopathological vessel-like structure similar to RCC and PR was seen in five out of nine cases in a retrospective study, the use of sunitinib is currently recommended (35). On the other hand, international retrospective studies on pazopanib reported that despite of 13 of 30 ASPS cases receiving the administration of other angiogenesis inhibitors during pretreatment, efficacy was confirmed in eight (one CR, seven PR and RR of 27%), indicating its usefulness (36). Angiosarcoma is a rare STS which predilection sites include the skin and soft tissues, especially the scalp. A Phase II trial demonstrated the efficacy of paclitaxel, which is recommended as a first-line agent (37). It is known that tumors induce the overexpression of VEGF, which indicated the potential efficacy of angiogenesis inhibitors and led to the recommendation of sorafenib, sunitinib, and bevacizumab (33). Although it was a retrospective examination, a 20% RR (8/40) was demonstrated for pazopanib, indicating an efficacy similar to paclitaxel (38). Solitary fibrous tumor (SFT) currently refers to the same tumor as hemangiopericytoma. Because it progresses slowly, even if there is metastasis, surgery is the fundamental form of treatment if possible. However, if surgery becomes impossible, chemotherapy is selected, and bevacizumab and temozolomide, or multi-kinase inhibitors (e.g., sunitinib and sorafenib) are recommended (33). The same multi-kinase inhibitor, pazopanib, has a high likelihood of being effective. Furthermore, an integrated analysis of pazopanib consisting of 76 successful cases with a PFS of more than 6 months and OS of more than 18 months, included major tissues types such as leiomyosarcoma or synovial sarcoma, as well as rare tissues such as angiosarcoma (4 out of 7 cases), ASPS (4 out of 7 cases), and SFT (4 out of 7 cases). This showed its potential for the treatment of minor tissues types of STS, although it may be difficult to confirm its effectiveness because of the limited number of cases. As such, within diverse STS cases, there are tissue types for which pazopanib should be actively used, and both a good RR and a long-term response duration of pazopanib can be expected.

Pazopanib for renal cell carcinoma
A Phase II clinical trial (VEG102616 study) evaluated the oral administration of 800 mg of pazopanib once a day in 225 patients...
with localized recurrence or metastatic RCC with clear cell type who were untreated or treated with one regimen of cytokine or a bevacizumab-containing regimen (Table 3) (39). Although the primary endpoint was changed from the PD rate at 16 weeks to the response rate (RR) in the interim analysis, the RR was 34.7% (95% CI: 28.4–40.9%) and the median PFS was 51.7 weeks (95% CI: 43.9–60.3). The major side effects were diarrhea (63%), fatigue (46%), hair depigmentation (43%), nausea (42%) and hypertension (41%), and 34 cases were discontinued because of toxicity (15%). In another prospective trial of 55 patients with metastatic clear cell renal carcinoma who developed resistance to sunitinib or bevacizumab as a first-line therapy, the RR was 27% (95% CI: 17–40%), the median PFS was 7.5 months (95% CI: 5.4–9%), and the median OS was 14.8 months (95% CI: 12.0–28.8) after 8 weeks of pazopanib administration (Table 3) (40). Major side effects included fatigue (64%), nausea (60%), diarrhea (53%) and hypertension (27%), and nine cases (16%) were discontinued because of toxicity. The results of these Phase II trials confirmed the efficacy of pazopanib, regardless of pretreatment. Moreover, the safety profile of pazopanib was considered to be acceptable, and its tolerability was confirmed.

Furthermore, according to an analysis of the PK/PD data of 205 cases in the VEG102616 study, the optimum cutoff value for the trough concentration according to PFS and tumor reduction rate was 20.5 μg/ml (43). Based on this cutoff value, the higher value group had significantly longer PFS than the lower value group (52 weeks vs. 19.6 weeks; P < 0.004) and the tumor RR was significantly higher (37.9% vs. 6.86%; P < 0.001). However, as blood concentration measurements are associated with problems of intraindividual variability, de Wit et al. attempted the therapeutic drug monitoring of pazopanib. However, even with dose adjustment, intraindividual variability could not be decreased (44). Furthermore, it is well known that food has a strong impact on intraindividual variability. Pazopanib tends to have a higher concentration in the blood of those with a high fat diet, especially when administered after eating a high fat meal compared with an empty stomach, with both the AUC and trough concentration increasing ~2-fold (45).

A total of 435 RCC patients (233 treatment-naïve cases and 202 cases treated with cytokine therapy), and those with progressive or metastatic clear cell types were randomly assigned to the pazopanib group (n = 290) or the placebo group (n = 145) at a ratio of 2:1. Stratification factors included the performance status (PS), prior nephrectomy, and prior systemic treatment (treatment-naïve or cytokine pretreated). A Phase III trial (VEG105192 study) with the primary endpoint of PFS, and secondary endpoints of OS, RR, response duration, and safety, was conducted (Table 3) (41). The median PFS was 9.2 months in the pazopanib group (95% CI: 7.4–12.9) and 4.2 months in the placebo group (95% CI: 2.8–4.2); it was significantly longer in the pazopanib group than in the placebo group (HR 0.46; 95% CI: 0.34–0.62). This significant extension of PFS in the pazopanib group was confirmed in a group without pretreatment and in a group with a history of cytokine treatment. The RR was significantly different between the pazopanib group (30%; 95% CI: 25.1–35.6) and the placebo group (3%); however, there was no significant difference in OS between the groups: the pazopanib group OS was 22.9 months (95% CI: 17.6–28.5) and the placebo group was 21.6 months (95% CI: 16.0–27.7) (46). The reason for this was that a crossover from placebo to pazopanib took place early, from only 6 weeks after randomization, and accounted for 54% of the placebo group, which was considered a high rate. As a result, pazopanib was administered for a long time after the crossover.

### Table 3. Effects of pazopanib on renal cell carcinoma and adverse events

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<th>Treatment</th>
<th>Number</th>
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<td>RR (%)</td>
<td>34.7% (95% CI: 29.0–40.9)</td>
<td>26% (95% CI: 21.3–31.5)</td>
<td>14% (95% CI: 9.4–18.8)</td>
<td>27% (95% CI: 22.3–32.4)</td>
<td>26% (95% CI: 21.3–31.5)</td>
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<td>PFS (95% CI)</td>
<td>51.7 weeks (95% CI: 43.9–60.3)</td>
<td>3.6 weeks (95% CI: 2.8–4.2)</td>
<td>14.1 weeks (95% CI: 11.2–17.0)</td>
<td>23.9 weeks (95% CI: 19.2–28.5)</td>
<td>3.6 weeks (95% CI: 2.8–4.2)</td>
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<td>OS (95% CI)</td>
<td>31 months (95% CI: 25.1–35.6)</td>
<td>8.2 months (95% CI: 6.7–9.7)</td>
<td>28.8 months (95% CI: 25.4–32.3)</td>
<td>22.9 months (95% CI: 17.6–28.5)</td>
<td>8.2 months (95% CI: 6.7–9.7)</td>
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RR, response rate; PFS, progression-free survival; OS, overall survival; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CI, confidence interval; NR, not reached; NC, not calculated; NE, not evaluated.
There was an extension study in which pazopanib was administered to patients who were assigned to the placebo group and became PD. A total of 80 patients were registered, resulting in a median PFS of 9.2 months (95% CI: 7.3–12.0), median OS of 23.5 months (95% CI: 16.3–28.0) and RR of 37.5% (95% CI: 26.9–48.1). Thus, the effects were similar to those in the above described Phase III trial (PEG105192 study) (47). The main side effects consisted of diarrhea (52%), hypertension (40%), hair color change (38%), nausea (26%), anorexia (22%) and vomiting (21%). The major adverse events of 3 Grade toxicity (CTCAE ver. 3.0) were diarrhea and hypertension. As abnormal test values, increased ALT and AST levels were identified in ≥50% of patients, whereas ≥3 Grade toxicity was identified in 10% of cases; however, by decreasing or interrupting pazopanib, ALT level was improved to Grade 1 in 87% of patients. Ultimately, toxicities (e.g., an increase in liver enzymes, diarrhea and thrombosis) led to the discontinuation of pazopanib in 16% of patients. A study on HR-QOL using EORTC QLQ-C30 and Euroqol 5 Dimension (EQ-5D) reported no significant difference between groups during 48 weeks of observation, but there was a smaller number of patients, whose HR-QOL decreased by ≥20% compared with baseline in the pazopanib group in a post hoc analysis. Furthermore, patients who experienced a response in the pazopanib group (CR/PR) did not show a significant decrease in HR-QOL compared with the cases without a response (48).

Compared with IFN-α, sunitinib exhibited prolonged PFS as a first-line treatment for advanced kidney cancer, whereas sorafenib did not (49,50). Similar to pazopanib, antitumor effects of sunitinib are primarily derived by blocking VEGF signaling; however, sunitinib is known to block more kinases than pazopanib (51). Drugs blocking multiple kinases cause several adverse events. Therefore, a comparative study was conducted to investigate which of the two drugs was the optimal first-line treatment for RCC. A Phase III trial (COMPARZ study) of 1110 patients with RCC who had a clear cell type without systemic treatment for progressive or metastatic RCC was conducted on the noninferiority of pazopanib relative to sunitinib by randomly assigning subjects into either the pazopanib group (n = 557) or the sunitinib group (n = 553) (Table 3) (42). The primary endpoint was PFS, and the upper limit of 95% CI for the hazard ratio (HR) of PFS in the Cox proportional hazard model of <1.25 (noninferiority margin) was considered to indicate noninferiority. The secondary endpoints were OS, objective response rate (ORR), response duration, HR-QOL and safety. As a result, in an intention to treat analysis, the median PFS was 8.4 months in the pazopanib group (95% CI: 8.3–10.9) and 9.5 months in the sunitinib group (95% CI: 8.3–11.1) with a hazard ratio of 1.047 (95% CI: 0.90–1.22). Noninferiority of pazopanib to sunitinib was confirmed. Meanwhile, noninferiority was not confirmed in the per-protocol analysis, though to a minor extent, complicating the interpretation of the results from this trial. ORR was 31% in the pazopanib group (95% CI: 26.9–34.5) and 25% in the sunitinib group (95% CI: 21.2–28.4), confirming a significant difference between the groups (P = 0.03). The median OS was 28.3 months in the pazopanib group (95% CI: 26.0–35.5) and 29.1 months in the sunitinib group (95% CI: 25.4–33.1), which were similar between the groups (HR: 0.92; 95% CI: 0.79–1.06) (52). The incidence rate of severe adverse events was 42% in the pazopanib group and 41% in the sunitinib group. In the pazopanib group, 135 patients (24%) were discontinued because of adverse events, with the main cause being increased liver enzyme levels and proteinuria. In the sunitinib group, 112 patients (20%) required treatment discontinuation due to fatigue, diarrhea, and proteinuria. Furthermore, HR-QOL was evaluated with four evaluation tools. During 6 months of treatment, 11 out of 14 items associated with HR-QOL were statistically more favorable in the pazopanib group than in the sunitinib group. In particular, indices of HR-QOL, pain in the mouth and throat, pain in hands and feet, and fatigue, were more favorable in the pazopanib group. Furthermore, a post-hoc analysis of quality-adjusted time without symptoms or toxicity (Q-TWIST) was performed as a qualitative adjustment analysis and revealed that the mean time spent in Grade 3 or 4 was clearly longer in the sunitinib group than in the pazopanib group (difference of 31 days [95% CI: 13–49]); thus, Q-TWIST was also longer in the pazopanib group (difference range from −11 days to 43 days) (53).

The PISCES trial was a unique clinical trial in which 169 patients were randomly assigned into the pazopanib group or sunitinib group and underwent treatment for 10 weeks (54). After a 2-week washout period, the patients switched to the other medication for 10 weeks. The patients were then asked which medication they preferred. The results showed that 70% of the patients preferred pazopanib. The main reason was a relatively good QOL and less fatigue. In addition, 22% selected sunitinib, while 8% had no preference. Furthermore, 50% of patients in the pazopanib group confirmed of not experiencing any fatigue compared with only 15% in the sunitinib group. Similarly, 45% of patients in the pazopanib group confirmed of no change in taste compared with only 10% in the sunitinib group. These results indicate that pazopanib has a higher tolerability than sunitinib, and that it is also preferred by most patients.

Regarding postoperative adjuvant chemotherapy, a Phase III trial (PROTECT study) was performed to examine postoperative adjuvant therapy with pazopanib for RCC patients with a high risk of recurrence following nephrectomy (55). The subjects comprised RCC patients with pT2 (high grade), ≥T3, or N1 clear cell type following nephrectomy, and were assigned to either the pazopanib group or the placebo group at a ratio of 1:1. Patients were administered pazopanib or placebo for 1 year. The primary endpoint was initially disease-free survival (DFS) for 800 mg of pazopanib. However, because of the presence of many discontinued cases due to toxicity, the pazopanib dose was decreased and the primary endpoint was changed to DFS for 600 mg pazopanib. Overall, there were 1538 registered cases, and the intent-to-treat (ITT)600 cohort included 403 patients (198 in the pazopanib group and 205 in the placebo group), whereas the ITT600 cohort included 1135 (571 in the pazopanib group and 564 in the placebo group). The results showed that DFS, the primary endpoint, of the ITT600 cohort, did not improve significantly (HR: 0.86; 95% CI: 0.70–1.06). The secondary endpoint, DFS of ITT600, showed a significant decrease in risk (HR: 0.69; 95% CI: 0.51–0.94). Long DFS was obtained in the group with a high trough value for plasma concentration (>20.5 μg/ml).

Adverse events were confirmed in 98% of patients in the pazopanib group and 90% in the placebo group in the ITT600 cohort. In particular, Grade 3 or 4 adverse events were confirmed in 60% of the pazopanib group and 21% of the placebo group. The main adverse events included diarrhea, hypertension and elevated ALT and AST levels. A reduction in the dose because of adverse events was confirmed in 48% of the 600 mg pazopanib group and 53% of the 800 mg pazopanib group and 35% and 39% of patients were discontinued because of adverse events. A group that had increased plasma concentration during the early stages showed a high incidence of adverse events. The QOL was evaluated with the Functional Assessment of Cancer Therapy-Kidney Symptom Index 19 and was decreased during treatment in the 600 mg pazopanib group compared with the
placebo group. These results suggest that even considering the toxicity and treatment response, pazopanib cannot be recommended as a postoperative adjuvant therapy for RCC. Previous studies have evaluated the efficacy of adjuvant chemotherapy with sunitinib and sorafenib, which are the molecular target drugs besides pazopanib. These studies have demonstrated extremely strong toxicity, a large number of treatment dropouts, and shorter OS (56,57). Although patient backgrounds in each trial differed, based on the results, few benefits outweigh the toxicity of adjuvant chemotherapy with pazopanib, sunitinib or sorafenib; these drugs are also not recommended in the guidelines.

However, pazopanib has been recommended as the first- and second-line treatment for clear cell type RCC with favorable/intermediate risk according to the Memorial Sloan Kettering Cancer Center classification based on past clinical trials, and is currently widely used in actual clinical settings. Although sunitinib is recommended as the first-line treatment, results of the COMPARZ trial and PISCES trial that compared these two drugs favored pazopanib from the perspective of QOL. However, in the COMPARZ trial, the QOL evaluation was performed on the 28th day of administration, just before the washout period of sunitinib, which was inappropriate for evaluating adverse events, because the evaluation might have favored pazopanib. The noninferiority margin of the COMPARZ trial was slightly high at 1.25, and the per-protocol analysis did not verify noninferiority. Thus, these findings have resulted in some criticism.

Regarding actual clinical settings, an extremely large-scale international retrospective study compared pazopanib (n = 919) and sunitinib (n = 6519) as the first-line treatment for 7438 patients with metastatic RCC (58). Although sunitinib was approved earlier than pazopanib and there was a difference in the number of cases, the median PFS adjusted by the International mRCC Database Consortium prognostic criteria was 8.3 months in the pazopanib group (95% CI: 7.2–8.9) vs. 8.4 months in the sunitinib group (95% CI: 8.2–8.7) (HR: 1.08; 95% CI: 0.98–1.19). The median OS was 22.6 months in the pazopanib group (95% CI: 21.1–24.7) vs. 22.3 months in the sunitinib group (95% CI: 21.4–23.2) (HR: 1.03; 95% CI: 0.92–1.17). The RR was 28% in the pazopanib group and 30% in the sunitinib group, which was not significantly different between the two groups. Because this was a retrospective analysis, the quality of research may be low; however, considering the result of this study was similar to that of the COMPARZ trial, although it included many advanced patients that may be ineligible in a normal prospective study, it is fair to say that pazopanib was as equally effective as the first-line therapy in a clinical setting. Similarly, pazopanib has shown a good response as a second-line treatment, and can be an option following cytokine therapy. Furthermore, in a retrospective study that summarized 1012 cases worldwide, pazopanib (n = 110) showed efficacy with a PFS of 4.6 months and OS of 13.7 months, similar to VEGFR-TKI as a salvage line (59).

The introduction of molecular targeting agents such as pazopanib has prolonged the OS of patients with RCC (60); however, it remains unclear which molecular targeting drug should be used, primarily because response predicting factors and biomarkers have not been identified. Furthermore, immuno-oncology (I-O) drugs are currently being used for various cancers. Nivolumab, an I-O drug, showed a longer OS than everolimus as a second-line treatment for advanced RCC following treatment with an angiogenesis inhibitor (CheckMate025 trial (61)), and b was ready-to-use in actual clinical settings. There are still many issues to be examined, and clinical trial results of I-O drugs, including their combined use with existing drugs might significantly change the chemotherapy of RCC. However, the importance of angiogenesis inhibitors, including pazopanib, is unlikely to change (62).

**Discussion**

Pazopanib is now considered an important treatment option for STS and RCC. However, although many clinical trials have investigated its efficacy for many other types of cancers, results were disappointing. For example, a Phase III trial evaluated pazopanib given as maintenance treatment following standard first-line platinum-based chemotherapy in patients with advanced non-small-cell lung cancer. However, it failed to improve the OS and PFS of non-small-cell lung cancer patients compared with placebo following a platinum-based therapy (63).

Generally, ~20% of patients in prospective clinical trials of pazopanib were discontinued because of toxicity, with liver dysfunction being a major adverse event that occurred in ~50% of cases. In nine meta-analyses of prospective clinical trials of pazopanib, 408 out of 2080 cases (20%) showed an increase in ALT levels that was >3-fold the upper limit of the normal range (ULN), whereas 294 cases (14%) showed an increase in AST levels of 3-fold than ULN (64). The incidence rate of increased AST/ALT was 8/7% for 3–5 × ULN, 5/4% for 5–8 × ULN, 5/3% for 8–20 × ULN, and 1/1% for 20 × ULN. The onset of an increase of ≥5 × ULN in ALT occurred mostly within 9 weeks (81%), with a median of 42 days. With a ≤2.5 × ULN, 89% of patients recovered within the median time until recovery, which was 30 days. In a multivariate analysis, patients aged ≥60 years tended to have a greater increase in ALT levels; thus, the administration of pazopanib to elderly patients requires more caution. A genetic pharmacological study was conducted on Caucasian patients who participated in Phase II and Phase III trials of pazopanib against RCC, and a correlation between gene polymorphisms of UDP-glucuronosyl transferase (UGT) 1A1 and hyperbilirubinemia was reported (65). Patients homozygous for UGT1A1*28 exhibited a higher incidence of hyperbilirubinemia than heterozygous or wild-type patients. Pazopanib has an UGT1A1-inhibitory action; thus, for patients with a gene polymorphism in which the expression of UGT1A1 was decreased, bilirubin excretion was delayed. If an indirect-bilirubin dominant increase in bilirubin is seen during treatment with pazopanib, such a possibility should also be taken into consideration.

Hypertension is also a major adverse event associated with pazopanib, occurring in ~40% of cases when mild cases were included. However, most cases were manageable. Hypertension caused by an angiogenesis inhibitor was correlated with treatment results, and was reported to be a potential biomarker of response prediction (66,67); however, another study reported no correlation (68), and thus, further discussion is necessary. A correlation between hypertension caused by pazopanib and treatment results has been examined in past Phase II and Phase III trials. Unfortunately, the results could not confirm a correlation in a study on STS (69) or RCC (70). Thus, increased blood pressure caused by pazopanib is an adverse event that should be treated, but cannot be a biomarker of response prediction.

Although relatively rare, pneumothorax caused by pazopanib has been occasionally reported. For example, the incidence of pneumothorax in sarcoma is relatively high (2%) (71). Similarly, the incidence of pneumothorax in the PALETTE study was 3% in the pazopanib group (8 out of 239 cases); thus, it is assumed that peripheral lung metastasis and necrosis of pleural metastasis associated with treatment or a natural course of pulmonary metastasis of sarcoma increases the incidence rate. However, other reports...
described a high incidence rate of 14% (6 out of 43 cases), and resistance to treatment of pneumothorax; therefore, a sufficient explanation before treatment and appropriate treatment following the onset of such symptoms are necessary (72).

Pazopanib is an extremely expensive drug, and its cost-effectiveness is currently being examined. For example, in the United Kingdom, if pazopanib is used as a second-line therapy for STS, the quality-adjusted life year (QALY) increases by 0.128 compared to the placebo, but the cost increases by £7976. As a result, the incremental cost-effectiveness ratio (ICER) of pazopanib versus the placebo was estimated to be £62 162 per QALY gained (73). In the United Kingdom, the threshold is generally £30 000 per QALY. Thus, compared to placebo, pazopanib is considered to poor cost-effectiveness, but it is still more cost-effective than other drugs used for STS (e.g., trabectedin, ifosfamide, and gemcitabine combined with docetaxel). Similarly, a Spanish study compared the cost-effectiveness with trabectedin, and reported that compared to trabectedin, pazopanib led to better health outcomes (0.705 vs. 0.686 QALY, Δ0.018), cost, administration method, and treatment cost of adverse events. As a result, the estimated overall cost was lower for pazopanib than trabectedin (£21 861 vs. £45 338, Δ£23 477) (74). Its cost-effectiveness as a first-line therapy for RCC was compared with sunitinib in the United Kingdom, where QALY was higher in the pazopanib group than in the sunitinib group (1.6026 vs. 1.5432 QALY, Δ0.0595), and the estimated overall cost was lower (£38 126 vs. £39 038, Δ£1061) (75). A probability sensitivity analysis estimated that the probability of pazopanib leading to a better QALY than with sunitinib was 76%; thus, the cost-effectiveness acceptability curve also demonstrated that pazopanib is more cost-effective than sunitinib. However, cost-effectiveness studies are strongly influenced by the medical environment of each country, and thus, the results from another country cannot be generally applied. However, these do not constitute reasons to hesitate to use pazopanib as a second-line treatment for STS or a first-line treatment for RCC.

Conclusions

Although pazopanib is associated with various adverse events, including liver dysfunction and hypertension, its appropriate use will allow continued treatment. Based on the results of past clinical trials, pazopanib should have a central role in the treatment of RCC and STS in the future. Further advancements in biomarker studies to elucidate the mechanisms of response predicting factors and resistance to pazopanib are expected to improve treatment results.

Conflict of interest statement

The authors declare that they have no conflict of interest.

References

Drug review: Pazopanib


