

Concise Drug Review: Pazopanib and Axitinib

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Key Words. Pazopanib • Axitinib • Drug profile • Angiogenesis • VEGF

Disclosures: Jan H.M. Schellens: Development of oral taxanes (IP); Merck, AstraZeneca, Roche (C/A); Roche, AstraZeneca (RF); Other: PI of sponsored trials of Roche, Merck, AstraZeneca, Eisai, Pfizer, Bayer, Novartis, GlaxoSmithKline. The other authors indicated no financial relationships.

Section Editors: Eddie Reed: (NIH, Bristol-Myers Squibb) (IP–Taxol patent); Ortho Biotech (H); Protea Biosciences (O); William D. Figg: None.

Reviewer “A”: Amgen, Janssen/Ortho Biotech, Sanofi (C/A); Janssen/Ortho Biotech, Sanofi (H)

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Identify the current indications for pazopanib and axitinib.
2. Describe the mechanism of action and the pharmacokinetics of pazopanib and axitinib.
3. Enumerate the clinical benefits of pazopanib and axitinib, and describe the position of these drugs in the treatment paradigm of metastatic renal cell cancer.

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ABSTRACT

Pazopanib and axitinib are both U.S. Food and Drug Administration approved ATP-competitive inhibitors of the vascular endothelial growth factor receptor. Pazopanib and axitinib have been shown to be effective and tolerable treatment options for patients with metastatic renal cell cancer and therefore have enlarged the armamentarium

for this disease. This concise drug review discusses the clinical benefits, clinical use, mechanism of action, bioanalysis, pharmacokinetics, pharmacogenetics, pharmacodynamics, drug resistance, toxicity, and patient instructions and recommendations for supportive care for these two drugs. *The Oncologist* 2012;17:1081–1089

INTRODUCTION

Pazopanib (Votrient®; GlaxoSmithKline, Brentford, U.K.) (Fig. 1A) is currently approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency for

the treatment of patients with metastatic renal cell carcinoma (mRCC) [1]. In the pivotal phase III study in patients with mRCC, pazopanib led to a clinically relevant and statistically significant longer progression-free survival (PFS) time of 5

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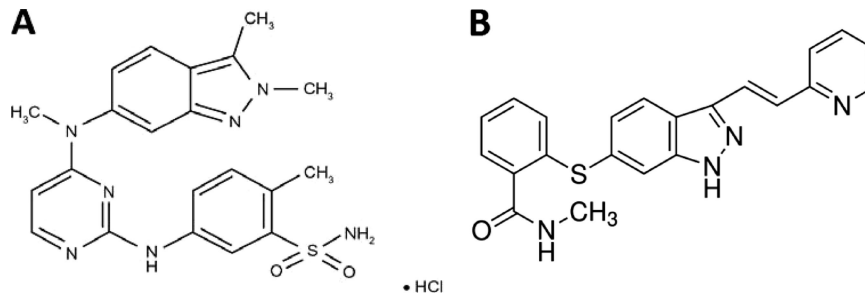


Figure 1. Chemical structures. (A): Chemical structure of pazopanib. (B): Chemical structure of axitinib.

months versus placebo, and it has been shown to provide clinical benefit in patients with various other tumor types, including soft tissue sarcoma, non-small cell lung cancer, ovarian cancer, and thyroid cancer [2–6]. Axitinib (Inlyta®; Pfizer Inc., New York) (Fig. 1B) was recently approved by the FDA for the treatment of patients with mRCC after failure of one prior systemic therapy. This approval followed the FDA advisory committees, who described the favorable benefit–risk profile of axitinib in patients with previously treated advanced RCC based on a comparative phase III trial of axitinib versus sorafenib [7, 8]. Pazopanib and axitinib are both small molecule angiogenesis inhibitors with similar drug profiles (Table 1). Pazopanib is being studied for additional indications in adults, including adjuvant treatment of renal cell cancer, advanced soft tissue sarcoma and ovarian cancer, whereas axitinib is being studied as a single agent as well as in combination with chemotherapy across several tumor types, such as hepatocellular carcinoma, pancreatic cancer, thyroid cancer, and advanced refractory non-small cell lung cancer [9]. Furthermore, a phase I pediatric dose-finding study of pazopanib is currently ongoing, and phase II and III pediatric trials have been planned [10].

CLINICAL BENEFITS

In a phase II study with pazopanib, 800 mg once daily (QD), in 225 patients with metastatic or locally recurrent RCC, an overall response rate of 34.7% (95% confidence interval [CI], 28%–41%) and a median PFS interval of 51.7 weeks were demonstrated. In a randomized placebo comparison ($n = 55$), the PFS interval was 11.9 months for pazopanib versus 6.2 months for placebo [11]. In the pivotal randomized phase III placebo-controlled clinical trial, pazopanib demonstrated a highly significant longer PFS time in both treatment-naïve and cytokine pretreated patients with mRCC. The median PFS interval for patients receiving pazopanib was 9.2 months, versus 4.2 months for patients in the placebo group, with a more pronounced difference in the treatment-naïve group (11.1 months versus 2.8 months) than in the cytokine-refractory group (7.4 months versus 4.2 months). These benefits, together with pazopanib's associated relatively low incidence of severe myelosuppression, hand–foot syndrome, stomatitis, and fatigue compared with the safety profile of other agents of this class, such as sunitinib, positions pazopanib as a therapeutic option for mRCC patients. However, studies directly comparing the activity and safety of pazopanib and other registered tyrosine

kinase inhibitors for mRCC are lacking. Results from an ongoing clinical trial comparing the efficacy and safety profiles of pazopanib and sunitinib are expected to further determine the position of pazopanib in the treatment of patients with mRCC [2, 12].

In a randomized, phase III clinical trial, axitinib was shown to benefit patients with mRCC after failure of one previous systemic therapy. Compared with sorafenib, axitinib led to a statistically significant and clinically meaningful longer PFS time (6.7 months versus 4.7 months; hazard ratio [HR], 0.665; one-sided $p < .0001$) in this study group. The median PFS times were 12.1 months for axitinib versus 6.5 months for sorafenib (HR, 0.464; $p < .0001$) for patients previously treated with cytokines and 4.8 months versus 3.4 months (HR, 0.741; $p = .0107$), respectively, for patients who were previously treated with sunitinib. The objective response rates were 19% for axitinib and 9% for sorafenib ($p = .001$), with median durations of response of 11 months for axitinib versus 10.6 months for sorafenib. The overall survival (OS) time was not significantly different between the two groups [8]. Furthermore, in phase II studies, axitinib was demonstrated to have antitumor activity in patients with cytokine-refractory and sorafenib-refractory mRCC, with objective response rates of 44% and 22.6%, median PFS times of 15.7 months and 7.4 months, and median OS times of 29.9 months and 13.6 months, respectively [13, 14]. The 5-year OS data from the phase II study with axitinib in patients with cytokine-refractory mRCC were presented recently. The median follow-up for OS evaluation was 5.9 years and the 5-year survival rate was 20.6% (95% CI, 10.9%–32.4%). Axitinib treatment can result in OS times >5 years in a subgroup of patients with mRCC and could therefore be considered as a treatment option for second-line therapy of mRCC [15].

CLINICAL USE

Pazopanib is available as film-coated tablets of 200 mg and 400 mg. The recommended dose is 800 mg QD, administered at least 1 hour before or 2 hours after food intake. The dose of pazopanib should be reduced to 400 mg QD in patients who also use strong cytochrome P450 (CYP)3A4 inhibitors, and a dose reduction of 75% is advised for patients with moderate hepatic impairment. Individual dose adaptations based on tolerability should be taken in steps of 200 mg [2, 16]. In a phase I study in children (aged 4–21 years) with relapsed or refrac-

tory solid tumors, the maximum-tolerated dose of pazopanib was 450 mg/m² [10].

Axitinib is available as 1 mg and 5 mg oral tablets, and the recommended starting dose is 5 mg twice daily (BID) on a continuous dosing schedule. The axitinib dose could be increased to 7 mg BID in patients who experience no adverse events grade >2, according to the Common Terminology Criteria for Adverse Events for ≥2 weeks, unless the patient's blood pressure is >150/90 mm Hg or the patient receives antihypertensive medication. Subsequently, the treatment dose could be further increased to 10 mg BID according to the same criteria. However, the clinical benefit of increasing the dose of axitinib in the treatment of patients with mRCC is yet to be defined in an ongoing phase II trial. If needed, the dose of axitinib could be decreased to 3 mg BID. If further dose reduction is necessary, the recommended dose is 2 mg BID [8, 17].

MECHANISM OF ACTION

Pazopanib and axitinib are second-generation potent inhibitors of multiple protein targets involved in tumor cell proliferation and angiogenesis. Angiogenesis plays a critical role in the progression of solid tumors as small as 1–2 mm in diameter. In this process, several proangiogenic factors are involved, with a central role for the vascular endothelial growth factor (VEGF) family. VEGF binds to the cell surface receptors VEGFR-1, VEGFR-2, and VEGFR-3, which subsequently leads to the recruitment of ATP. ATP in turn binds to the so-called ATP-binding pocket of VEGFR, causing activation of the VEGF signaling pathway, which ultimately results in cellular effects that are pivotal for angiogenesis. Inhibition of this pathway has demonstrated antitumor activity in several tumor types, including RCC, colorectal cancer, breast cancer, and non-small cell lung cancer [18]. Pazopanib inhibits this signaling pathway via ATP-competitive inhibition of VEGFR-1, VEGFR-2, and VEGFR-3, with in vitro 50% inhibitory concentrations of 10 nm, 30 nm, and 47 nm for VEGFR-1, VEGFR-2, and VEGFR-3, respectively. Similar activity was demonstrated against platelet-derived growth factor receptor (PDGFR)- α , PDGFR- β , fibroblast growth factor receptor (FGFR)-1, FGFR-3, and c-Kit. The transmembrane glycoprotein receptor tyrosine kinase (c-Fms) is inhibited as well, but with modest potency [19, 20]. Axitinib is a more selective tyrosine kinase inhibitor because it only shows activity against VEGFR-1, VEGFR-2, and VEGFR-3. Furthermore, its potency in vitro is higher than that of pazopanib and the first-generation VEGFR inhibitors such as sunitinib and sorafenib [8, 21, 22]. Additionally, in contrast to first-generation inhibitors, axitinib has no substantial inhibitory effect on PDGFRs, B-Raf, c-Kit, and Flt-3, which might contribute to less off-target adverse effects and a better therapeutic window [8].

BIOANALYSIS

Bioanalysis of pazopanib and axitinib can be exerted by high-performance liquid chromatography with tandem mass spectrometry [23, 24].

PHARMACOKINETICS

Absorption

At the recommended dose of 800 mg pazopanib QD, the maximum plasma concentration (C_{\max}) after the first dose of $\sim 19 \pm 13$ $\mu\text{g/mL}$ is reached after 2–4 hours, and a geometric mean area under the plasma concentration–time curve (AUC) from time zero extrapolated to infinity ($\text{AUC}_{0-\infty}$) of $\sim 650 \pm 500$ $\mu\text{g}\cdot\text{h/mL}$ is obtained. Continuous dosing at 800 mg QD results in a mean AUC of 1,037 $\mu\text{g}\cdot\text{h/mL}$ and a C_{\max} of 58.1 $\mu\text{g/mL}$. The mean steady-state concentration (C_{trough}) was ≥ 15 $\mu\text{g/mL}$, which appeared to correlate with clinical activity in patients with mRCC. Pazopanib doses >800 mg QD are not likely to produce higher plasma concentrations [16, 19, 24]. Systemic exposure to pazopanib did not increase in a dose-proportional manner in a phase I dose-escalation study in patients with hepatocellular carcinoma, and ranged from 151 $\mu\text{g}\cdot\text{h/mL}$ at 200 mg pazopanib QD to 214 $\mu\text{g}\cdot\text{h/mL}$ at 800 mg pazopanib QD. The mean C_{\max} values for the pazopanib doses used in this study also did not show linear pharmacokinetics and were 29.8 g/mL at 200 mg QD, 31.6 g/mL at 400 mg, 28.8 g/mL at 600 mg QD, and 39.5 g/mL at 800 mg QD. C_{trough} levels were >15 $\mu\text{g/mL}$ for all doses and were highest at the 800-mg pazopanib QD dose, that is, 28.1 $\mu\text{g/mL}$ [25]. Administration of pazopanib with both low- and high-fat meals resulted in an approximately twofold higher systemic exposure, as indicated by twofold greater AUC and C_{\max} values. Pazopanib should therefore be administered to patients in the fasted state, at least 2 hours after or at least 1 hour before food intake [26]. Administration of a single 400-mg pazopanib tablet crushed resulted in an approximately twofold higher C_{\max} and a shorter t_{\max} (by ~ 2 hours) than with administration of the whole tablet [27].

After oral administration in the fed state, axitinib is rapidly absorbed from the gut, with peak plasma levels occurring within 2–6 hours after intake [28]. The rate and extent of drug absorption are higher in an overnight fasted state, with peak plasma concentrations occurring 0.5–4 hours post dosing [28–30]. At the recommended dose of 5 mg BID, the mean C_{\max} and AUC_{0-24} levels after the first dose are 37 ng/mL and 188 ng·h/mL, respectively, in the overnight fasted state versus 22 ng/mL and 194 ng·h/mL, respectively, in the fed state. These data indicate a food effect on the pharmacokinetics of axitinib. Further studies, however, have confirmed that overnight fasting is not required, and administration of axitinib with food is recommended [28, 31]. At doses of 2–10 mg BID, axitinib exhibits linear pharmacokinetics, and steady state is reached within 15 days, with no unexpected accumulation [28].

Protein Binding

Both pazopanib and axitinib are highly protein bound (>99%). In vitro studies demonstrated that axitinib binds mostly to albumin and, more restrictively, to α -1-acid glycoprotein [16, 32].

Metabolism

Results from in vitro studies demonstrated that pazopanib is metabolized by CYP3A4 and, to a lesser degree, by CYP1A2

and CYP2C8. Only 6% of the exposure in plasma represents the four principle pazopanib metabolites. One of these metabolites, GSK1268997, showed potency similar to that of pazopanib in vitro employing human umbilical vein endothelial cells, whereas the other metabolites are 10- to 20-fold less active [19, 33].

In vitro metabolism studies showed that axitinib metabolism consists primarily of oxidation via CYP3A4 and, to a lesser extent, via CYP2C19 and CYP1A2, with additional metabolism occurring by glucuronidation via diphosphate glucuronosyltransferase (UGT)1A1. The main metabolites of axitinib, a sulfoxide and an N-glucuronide, are inactive [28, 31].

Elimination

After administration of the recommended dose of 800 mg, elimination of pazopanib occurs slowly at a mean terminal plasma half-life ($t_{1/2}$) of ~31 hours [24]. Elimination of pazopanib and its metabolites occurs primarily via the feces and $\leq 4\%$ of the orally administered dose is eliminated via renal excretion [19].

The $t_{1/2}$ of axitinib is 2–5 hours, with hepatobiliary excretion being the major elimination pathway. Approximately 30%–60% of orally administered axitinib is eliminated in the feces, with renal elimination accounting for a further 23%. The predominant component of eliminated axitinib in feces is unchanged axitinib, whereas in urine $< 1\%$ of the administered dose was found as unchanged drug [28, 32, 34].

Drug Interactions

Because pazopanib and axitinib are largely metabolized by CYP3A4, coadministration of agents known to be potent inducers or inhibitors of the CYP3A4 isozyme should be avoided. A study examining the concomitant administration of rifampicin, a potent inducer of CYP3A4, CYP1A2, and UGT1A1, and axitinib in healthy volunteers demonstrated 79% and 71% lower, respectively, geometric mean $AUC_{0-\infty}$ and C_{max} values of axitinib [30]. Furthermore, data from a single patient demonstrated that, after concomitant use of phenytoin, a potent inducer of multiple CYP450 enzymes, the AUC_{0-24} and C_{max} of axitinib were ~10-fold lower. Despite earlier clinical evidence of response to axitinib, this lower plasma exposure and C_{max} subsequently resulted in disease progression, which led to discontinuation from study treatment [28].

A phase I study examining the influence of ketoconazole, a potent CYP3A4 inhibitor, on the pharmacokinetics of axitinib demonstrated that concurrent administration of ketoconazole resulted in higher geometric mean AUC_{∞} and C_{max} values of axitinib by twofold and 1.5-fold, respectively [29].

Concurrent administration of 1,500 mg lapatinib, a substrate for and weak inhibitor of CYP3A4 and P-glycoprotein (P-gp) and a potent inhibitor of breast cancer resistance protein (BCRP), with 800 mg pazopanib resulted in a greater systemic exposure of pazopanib, with 50%–60% higher AUC_{0-24} and C_{max} values [35]. This greater pazopanib exposure is likely the result of P-gp and/or BCRP inhibition by lapatinib. Combina-

tion with strong P-gp and BCRP inhibitors and inducers should therefore be avoided [19].

Pazopanib itself is also able to inhibit several CYP enzymes, including CYP3A4, BCRP, P-gp, and organic anion transporter polypeptide (OATP)1B1. For example, coadministration of pazopanib (800 mg QD) and paclitaxel (80 mg/m²), a CYP3A4 and CYP2C8 substrate, once weekly resulted in higher AUC and C_{max} values for paclitaxel, of 45% and 40%, respectively [36]. Care should therefore be taken when pazopanib is coadministered with other oral CYP3A4, BCRP, P-gp, and OATP1B1 substrates [19].

Alterations with Disease or Age

Although limited data are available on the use of pazopanib in patients aged ≥ 65 years, no clinically significant differences in the safety of pazopanib were observed in patients of different ages [19]. In patients with moderate hepatic impairment, as indicated by elevated bilirubin and aminotransferases, pazopanib clearance was 50% lower, resulting in twofold higher AUC and C_{max} values than in individuals with normal hepatic function [37]. It is therefore recommended that patients with hepatic abnormalities be treated initially according to the pazopanib doses mentioned in Table 2. The starting dose of pazopanib should be reduced to 200 mg QD in patients with moderate hepatic impairment, and in patients with severe hepatic impairment pazopanib is contraindicated [19].

Currently, no age-related influences on the pharmacokinetics of axitinib have been reported, and information about the potential effects of diseases on its pharmacokinetics and pharmacodynamics is limited. In a phase I study evaluating the effects of hepatic impairment, as indicated by the Child-Pugh classification, on the pharmacokinetics and safety of a single oral dose of axitinib, individuals with mild hepatic dysfunction had pharmacokinetics similar to those of individuals with normal hepatic function. Patients with moderate hepatic impairment, however, had higher axitinib exposure than patients with normal hepatic function, as indicated by an approximately twofold higher $AUC_{0-\infty}$. The effect of severe hepatic impairment was not evaluated in that study. However, it can be reasonably expected to exceed or equal the effect of moderate hepatic dysfunction [32]. The recommended initial doses of axitinib are listed in Table 2. After the initial dose, subsequent doses can be increased or decreased based on individual safety and tolerability.

To date, no dedicated renal impairment trials for pazopanib and axitinib have been conducted. However, renal impairment is unlikely to significantly affect the pharmacokinetic properties of either drug because $< 4\%$ of orally administered pazopanib is eliminated via renal excretion, and after oral administration of axitinib no renal elimination of unchanged drug could be found [17, 19]. Furthermore, based on the pharmacokinetic analysis, no significant difference in clearance of either compound was observed in patients with mild to severe renal impairment [16, 17].

Table 1. Summary table		
Generic name(s)	Pazopanib	Axitinib
Commercial name(s)	Votrient®	Inlyta®
Molecular weight	437.52 g/mol	386.47 g/mol
Mechanism of action	ATP-competitive inhibition of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- α , PDGFR- β , c-Kit, FGFR-1, FGFR-3, Itk, Lek, c-Fms	ATP-competitive inhibition of VEGFR-1, VEGFR-2, VEGFR-3
Route of administration	Oral	Oral
Bioavailability	Variable, 14%–39%	Variable, ~58%
Protein binding (%)	>99%	>99%
Metabolism	Mainly via CYP3A4 with minor contribution from CYP1A2 and CYP2C8	Primarily via CYP3A4 and CYP3A5, and to a lesser extent via CYP1A2 and CYP2C19, and by glucuronidation via UGT1A1
Elimination	Primarily via feces, and <4% via renal elimination	Fecal elimination (via hepatobiliary secretion), 30%–60%; renal elimination, 23%
Terminal half-life	31 hours	2–6 hours
Main toxicities	Diarrhea, hypertension, hair color changes, nausea, anorexia, vomiting. Laboratory abnormalities: elevated ALT/AST, increased glucose, increased total bilirubin, leukopenia, proteinuria	Diarrhea, hypertension, fatigue, nausea, decreased appetite, dyspnea, dysphonia. Laboratory abnormalities: elevated creatinine, anemia, hypocalcemia lymphopenia, proteinuria
Pharmacogenetics	<i>UGT1A1</i> polymorphism is associated with pazopanib-induced hyperbilirubinemia; polymorphisms in <i>IL-8</i> , <i>HIF-1A</i> , <i>NR1I2</i> , and <i>VEGFA</i> may predict treatment response	Polymorphisms analyzed in CYP isozymes UGT1A1, ABCB1, and OATP1B1 were of no significant relevance in predicting pharmacokinetic variability
Resistance	Will develop as a result of amplification of proangiogenic genes, secretion of multiple proangiogenic factors, recruitment of proangiogenic bone marrow-derived cells, and escape mechanisms via different modes of vascularization	See pazopanib
Unique features		Selective inhibition of VEGFRs
Main drug interactions	Strong CYP3A4, P-gp, and BCRP inhibitors; CYP3A4, P-gp, and BCRP inducers and substrates; OATP1B1 substrates (e.g., statins)	CYP3A4 inhibitors, inducers, and substrates, e.g., ketoconazole, rifampicin, carbamazepin, cyclosporine, and simvastatin
Dose adaptations	Reduce dosage to 200 mg QD in patients with moderate hepatic impairment; reduce dosage to 400 mg QD if concomitant use of a strong CYP3A4 inhibitor is warranted; strong CYP3A4 inducers should not be used	Dose reduction of 50%–75% may be necessary in patients with moderate (or worse) hepatic impairment or with concomitant use of strong CYP3A4 inhibitors
Recommendations for supportive care	Monitor blood pressure frequently; treat mild to moderate hypertension with standard antihypertensive therapy; consider omitting pazopanib in patients experiencing severe or persistent hypertension. Monitor liver biochemistry, thyroid function, and urine protein periodically throughout treatment.	See pazopanib
Abbreviations: ABC, ATP-binding cassette; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCRP, breast cancer resistant protein (ABCG2); CYP, cytochrome P450; FGFR, fibroblast growth factor receptor; HIF-1A, hypoxia-inducible factor 1 α ; IL-8, interleukin 8; Itk, interleukin-2 receptor inducible T-cell kinase; Lek, leukocyte-specific protein tyrosine kinase; NR1I2, nuclear receptor subfamily 1, group I, member 2; OATP, organic anion transporter polypeptide; PDGFR, platelet-derived growth factor receptor; P-gp, P-glycoprotein; QD, once daily; UGT, uridine diphosphate glucuronosyltransferase; VEGFR, vascular endothelial growth factor receptor.		

Table 2. Pazopanib and axitinib starting dose in patients with hepatic impairment

Impairment	Pazopanib			Axitinib	
	Bilirubin	ALT	Starting dose	Child-Pugh Class	Starting dose
Mild	≤ULN >1–1.5× ULN	>ULN Regardless	800 mg	A	5 mg
Moderate	>1.5–3× ULN	Regardless	200 mg	B	2 mg
Severe	>3× ULN	Regardless	Contraindicated	C	Not studied

Abbreviations: ALT, alanine aminotransferase; ULN, upper limit of normal.

PHARMACOGENETICS

Because metabolism of pazopanib and axitinib occurs principally via CYP isozymes, polymorphisms in genes encoding these enzymes might contribute to the pharmacokinetic variability of these compounds. Next to CYP isozymes, axitinib is also a substrate for UGT1A1 and the drug transporters P-gp, encoded by the *ABCB1* gene, and OATP1B1, encoded by *SLC01B1*, which are also potential contributors to the interpatient variability in the pharmacokinetics of axitinib. However, in a meta-analysis using data pooled from 11 clinical pharmacological trials in healthy volunteers, none of the 15 polymorphisms analyzed were of significant relevance in explaining axitinib pharmacokinetic variability. Genotype-based dose adjustment is therefore not warranted after patients have been started on the initial dose of 5 mg BID [38].

Also for pazopanib, *CYP3A4* polymorphisms have no known effect on the pharmacokinetics of this compound. However, in a study examining 27 single nucleotide polymorphisms in 13 genes in 397 mRCC patients receiving pazopanib, polymorphisms in the genes encoding interleukin 8 (*IL-8*), hypoxia-inducible factor 1 α (*HIF-1A*), nuclear receptor subfamily 1, group I, member 2 (*NR1I2*), and VEGFA showed significant associations with PFS outcomes, when compared with wild-type genotypes [39]. Validation of these results is now ongoing to evaluate if these germline genetic markers can be used as predictive markers of the likelihood of response. In a preclinical in vivo study examining the effects of different *B-Raf* genotypes on the antitumor activity of pazopanib, significant differences were found among several xenograft tumor models. Only cell lines exhibiting either exon 11 mutations of *B-Raf*, human epidermal growth factor receptor 2 overexpression, or multiple pazopanib targets demonstrated a significant antiangiogenic response to pazopanib treatment. This result indicates a significant role for B-Raf in angiogenesis and suggests that B-Raf status might be a predictive marker for pazopanib efficacy [40].

DRUG RESISTANCE

Mechanisms of resistance to antiangiogenic therapy include amplification of proangiogenic genes, secretion of multiple proangiogenic factors (e.g., angiopoietin, VEGF(R), and ephrins), recruitment of proangiogenic bone marrow-derived cells, and escape mechanisms via different modes of vascularization [41]. The first three mechanisms ultimately result in greater levels of VEGF. Higher VEGF and VEGFR levels

might lead to specific angiogenic inhibitor-related toxicities and faster regrowth of the tumor vasculature when the anti-VEGF drug is discontinued [42, 43].

PHARMACODYNAMICS

The relationship between the dose of axitinib and response has not been extensively explored. In one study, the pharmacodynamic response to treatment with axitinib was measured by dynamic contrast-enhanced magnetic resonance imaging. Indicators of vascular response, such as the volume transfer constant (K^{trans}), which correlates with tumor vascular permeability and perfusion, and initial AUC (IAUC), were calculated to examine the effect of axitinib treatment on tumor vascular function. By day 2 of therapy, 50% decreases in K^{trans} and IAUC were demonstrated, which persisted through week 4 of treatment and corresponded to a plasma $AUC_{0-24} > 200$ ng·h/mL. Furthermore, both the K^{trans} and IAUC percentage changes correlated in a linear manner with the AUC_{0-24} and C_{max} levels of axitinib in plasma [44]. Another study retrospectively examined the correlation between diastolic blood pressure (DBP) and antitumor response to axitinib. That study demonstrated that patients with at least one DBP measurement ≥ 90 mm Hg during therapy had a significantly lower relative risk for death than patients with DBP < 90 mm Hg throughout therapy (HR, 0.55; $p < .001$). The relative risk for progression was lower in patients with a DBP measurement ≥ 90 mm Hg, and the objective response rate was significantly higher (43.9% versus 12%; $p < .001$). Furthermore, the median PFS interval (10.2 months versus 7.1 months) and median OS time (25.8 months versus 14.9 months) were greater for patients with a DBP measurement ≥ 90 mm Hg [45]. Additional studies to examine the pharmacodynamics of axitinib are currently ongoing.

The pharmacokinetic–pharmacodynamic relationships of pazopanib have not been extensively studied either. In a phase II trial, the relationship between plasma concentrations of pazopanib and drug exposure was investigated in 205 patients after 4 weeks and 12 weeks of treatment. Patients with a plasma concentration of pazopanib ≥ 20.6 $\mu\text{g/mL}$ ($n = 143$) at week 4 had a median PFS time of 49.4 weeks and patients with a plasma concentration < 20.6 $\mu\text{g/mL}$ at week 4 had a median PFS time of 20.3 weeks ($n = 62$; $p = .0041$). The overall response rates in these patients were 45% versus 18% ($p = .000017$). Plasma levels of pazopanib ≥ 20.6 $\mu\text{g/mL}$ may therefore be associated with better efficacy [46]. However, this needs to be proven in prospective studies. Furthermore, results

Table 3. Common treatment-emergent all-causality adverse events in the pivotal phase III trials

Pazopanib (n = 290)					
Adverse event	All grades, %	≥Grade 3, %	Laboratory abnormalities	All grades, %	≥Grade 3, %
Diarrhea	52	4	ALT increase	53	12
Hypertension	40	4	AST increase	53	8
Hair color changes	38	<1	Hyperglycemia	41	<1
Nausea	26	<1	Leukopenia	37	0
Anorexia	22	2	Total bilirubin increase	36	4
Vomiting	21	2	Hypophosphatemia	34	4
Fatigue	19	2	Neutropenia	34	1
Asthenia	14	3	Hypocalcemia	33	3
Abdominal pain	11	2	Thrombocytopenia	32	1
Headache	10	0	Lymphopenia	31	4
			Hyponatremia	31	5
			Hypoglycemia	17	<1
			Hypomagnesemia	11	4
Axitinib (n = 359)					
Adverse event	All grades, %	≥Grade 3, %	Laboratory abnormalities	All grades, %	≥Grade 3, %
Diarrhea	55	11	Creatinine elevation	55	0
Hypertension	40	16	Hypocalcemia	39	1
Fatigue	39	11	Anemia	35	<1
Decreased appetite	34	5	Lymphopenia	33	3
Nausea	32	3	Lipase elevation	27	5
Dysphonia	31	0	Thrombocytopenia	15	<1
Hand-foot syndrome	27	5	Hypophosphatemia	13	2
Weight decreased	25	2	Hemoglobin elevation	10	0
Vomiting	24	3	Neutropenia	6	1
Asthenia	21	5	Hypercalcemia	6	0
Constipation	20	1			
Hypothyroidism	19	<1			
Mucosal inflammation	15	1			

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

of a phase I study of pazopanib in patients with advanced tumors suggested that hypertension may represent a general pharmacodynamic marker of the activity of pazopanib. Further research, however, is necessary to examine the clinical relevance of this finding [24]. In a phase II study with pazopanib in patients with RCC, no significant correlation was observed between the 12-week treatment response and the von Hippel-Lindau status or the status of other soluble markers including sVEGFR-1, VEGF, and circulating endothelial cells [47].

TOXICITY

Chronic administration of axitinib and pazopanib is associated with manageable toxicities and a low rate of treatment discontinuation. The most common adverse events (all grades) reported in clinical trials with axitinib were diarrhea, hypertension, fatigue,

nausea, decreased appetite, dyspnea, dysphonia, hand-foot syndrome, and decreased weight [8, 14, 28]. In the pivotal phase III trial of pazopanib, diarrhea, hypertension, hair color changes, nausea, anorexia, and vomiting were the most common adverse reactions (all grades). The most frequent adverse events of grade ≥ 3 were hypertension (16%), diarrhea (11%), and fatigue (11%), during treatment with axitinib, and hypertension (4%), diarrhea (3%), and asthenia (3%), during treatment with pazopanib. Creatinine elevation (55%), hypocalcemia (39%), anemia (33%), lymphocytopenia (33%), and lipase elevation (27%) were the most frequently reported laboratory abnormalities (all grades) in the pivotal phase III trial of axitinib, whereas alanine aminotransferase or aspartate aminotransferase increases (53%), hyperglycemia (41%), leukopenia (37%), total bilirubin increases (36%),

and neutropenia (34%) accounted for the most common laboratory abnormalities during pazopanib treatment (Table 3) [2, 8].

PATIENT INSTRUCTIONS AND RECOMMENDATIONS FOR SUPPORTIVE CARE

Pazopanib should be administered without food and the tablet must not be crushed. Axitinib may be taken with or without food. Because hypertension is a frequently occurring adverse reaction associated with both drugs, blood pressure should be monitored frequently. Mild to moderate hypertension should be treated with standard antihypertensive therapy and axitinib or pazopanib treatment may be continued. In patients who experience severe or persistent hypertension while using antihypertensive therapy, discontinuation of axitinib or pazopanib should be considered [13, 14, 16, 17]. Neither compound should be used during pregnancy because this may cause fetal harm, and men and women should use effective birth control during treatment with pazopanib or axitinib, because both drugs are teratogenic. Because pazopanib and axitinib may increase serum levels of transaminases and bilirubin, liver biochemistry should be measured before treatment initiation and regularly during treatment. Additionally, monitoring of thyroid function and urine protein is recommended during treatment with both pazopanib and axitinib [16, 17].

CONCLUSIONS

Pazopanib and axitinib are both FDA-approved ATP-competitive VEGFR inhibitors and represent treatment options for pa-

tients with mRCC. The efficacy of pazopanib appears to be comparable with that of sunitinib, one of the main treatment options for patients with mRCC, and it may have a better tolerability profile. Therefore, pazopanib appears to be a valuable addition to the treatment of mRCC patients. However, results from head-to-head comparative studies, such as the Pazopanib Versus Sunitinib in the Treatment of Subjects With Locally Advanced and/or Metastatic Renal Cell Carcinoma clinical trial, are to be awaited to make a definitive statement about the position of pazopanib in relation to other medications for mRCC.

Compared with sorafenib, axitinib resulted in a longer PFS time, higher objective response rate, and longer OS duration in previously treated patients with mRCC. This makes axitinib a treatment option for second-line therapy of mRCC, and ongoing clinical trials have to determine the suitability of axitinib in the first-line setting. To conclude, pazopanib and axitinib, together with other recently approved drugs, including sorafenib, sunitinib, temsirolimus, everolimus, and bevacizumab, altered the treatment paradigm of mRCC and offer patients multiple treatment options.

AUTHOR CONTRIBUTIONS

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