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REVIEW

Axitinib in Metastatic Renal Cell Carcinoma

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ABSTRACT

Targeted agents have revolutionized the management of metastatic renal cell carcinoma (RCC). Axitinib, an inhibitor of vascular endothelial growth factor receptor (VEGFR), has been an important addition to currently available therapies for advanced RCC. Its ability to inhibit VEGFRs at nanomolar concentrations distinguishes it as a potent tyrosine kinase inhibitor, with increased selectivity for VEGFR-1, 2, and 3 at clinically applicable concentrations. The phase 3 AXIS trial has established its superiority in prolonging progression-free survival (PFS) in previously treated RCC patients (median PFS 6.7 months for axitinib vs. 4.7 months for sorafenib). Common toxicities of axitinib include hypertension, diarrhea, nausea, hand-foot syndrome, fatigue, and hypothyroidism. Axitinib-induced diastolic blood pressure elevation may be associated with improved clinical outcome, likely reflecting the "on-target" effect of axitinib. Dose escalation to achieve therapeutic plasma drug levels is of considerable clinical interest. Although axitinib has established efficacy in patients treated with one previous agent, its use in the frontline setting is currently the subject of ongoing research.

Keywords: Advanced renal cell carcinoma; Axitinib; Oncology; Pharmacodynamics; Progression-free survival; Vascular endothelial growth factor receptor

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INTRODUCTION

The treatment of metastatic renal cell carcinoma (mRCC) has historically included immunotherapy, although targeted agents have revolutionized treatment strategies over the last several years. The management of mRCC has evolved rapidly since 2005, when sorafenib, a tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptor (VEGFR),

was approved for advanced RCC following a phase 3 study in patients who had failed to respond to prior systemic therapy [1, 2]. Since then, newer VEGFR inhibitors, including sunitinib and pazopanib, have been approved in advanced renal cell carcinoma (RCC) in 2006 and 2009, respectively [3–5]. Additionally, bevacizumab, a monoclonal antibody to circulating vascular endothelial growth factor (VEGF), was approved in 2009 for mRCC patients in combination with interferon alpha [6, 7]. Newer, more biochemically potent VEGF-TKIs, such as axitinib, have expanded the armamentarium of available drugs with targeted action and established efficacy in mRCC.

Angiogenesis and neovascularization are key to proliferation and dissemination of neoplastic cells in many solid tumors. In sporadic RCC, mutations in the Von Hippel-Lindau (VHL) gene lead to decreased degradation of hypoxia-inducing factor (HIF), and subsequent upregulation of VEGF expression [8]. VEGF, a mitogen of endothelial cells, promotes angiogenesis and vascular permeability. Additionally, it also induces expression of plasminogen activators and metalloproteinases; thereby, promoting a prodegradative environment, facilitating cellular migration and invasion [9]. Downstream signaling upon activation of VEGFRs has also been associated with inhibition of apoptosis and decreased production of nitric oxide [10]. Thus, the VHL-HIF pathway is pivotal to the pathobiology of RCC, and has been crucial in the development of targeted agents that include VEGFR inhibitors as well as antibodies to circulating VEGF. Furthermore, mammalian target of rapamycin (mTOR) molecules that are downstream of phosphoinositide 3-kinase and protein kinase B pathways have also demonstrated an increased concentration of HIF-alpha; thus, playing a significant role in angiogenesis [11]. This has expanded available molecular targets and led to the development of mTOR inhibitors, temsirolimus and everolimus, which have demonstrated efficacy in mRCC [12, 13].

Since its Food and Drug Administration (FDA) approval in January 2012, the receptor selectivity, potency, high objective response rate (ORR), and tolerability of axitinib have generated considerable interest. The clinical evidence supporting the current role of axitinib in the management of mRCC is reviewed in this article, with a special emphasis on its place in current treatment regimens. In addition, management of drug toxicities and ongoing investigational trials centered on axitinib are detailed.

METHODS

A PubMed search was conducted using the key terms “axitinib” and “renal cell cancer.” Additionally, proceedings from major congresses in North America and Europe over the last 5 years were reviewed for abstracts related to axitinib in RCC.

MECHANISM OF ACTION

Axitinib is a second-generation, indazole-derived molecule that inhibits VEGFR-1, 2, and 3 at therapeutic plasma concentrations; thereby, blocking VEGF-mediated angiogenesis, cellular adhesion, migration, and eventually resulting in cellular apoptosis. Axitinib binds selectively to the adenosine triphosphate (ATP)-binding intracellular domain of VEGFR-1, 2, and 3 at nanomolar concentrations, stabilizing an inactive confirmation of these kinases and, thus, inhibiting downstream signal transduction [14, 15]. In fact, the half maximal inhibitory concentration (IC50) of axitinib for VEGFR-1, 2, and 3 inhibition is 0.1, 0.2, and 0.1–0.3 nM, respectively, distinguishing it as the

most potent VEGFR-1 inhibitor for the treatment of mRCC [16]. Despite platelet-derived growth factor receptor and C-Kit inhibitory effects observed in vitro, axitinib's potency against non-VEGF receptors is about eight-times weaker and, at clinically achieved plasma levels, VEGF inhibition alone is believed to be responsible for the observed clinical benefits [10]. This selectivity is likely responsible for the potent "on-target" effect and toxicity profile of this agent.

CLINICAL DATA

In the first phase 1 study of axitinib, 36 patients with advanced solid malignancies were treated with axitinib with total daily dose varying from 10–60 mg [17]. This trial helped define the maximal tolerated dose of axitinib as 5 mg orally twice a day (b.i.d.). Important dose-limiting toxicities included hypertension, diarrhea, and stomatitis. The incidence and severity of hypertension were proportional to drug dosage. Linear pharmacokinetics were observed in the dose range evaluated in this trial. Subsequent phase 1 studies conducted among Japanese and Chinese patients have confirmed similar pharmacokinetics and the adverse-effect profile of axitinib in non-Caucasian subjects [18, 19]. Another phase 1 study of axitinib in 12 Japanese patients confirmed the tolerability and efficacy of this dose, and demonstrated a significant correlation between axitinib exposure and decline in soluble VEGFR-2 levels [20].

Three independent phase 2 trials subsequently evaluated the role of axitinib in mRCC patients refractory to prior therapy (Table 1) [21–23]. In the initial single-arm phase 2 study published in 2007, 52 mRCC patients with a performance status of Eastern Cooperative Group 0–1, who had previously failed to respond to cytokine therapy, were assigned to receive axitinib starting at 5 mg b.i.d. [21]. The primary endpoint was ORR. The median age of the cohort was 59 years, and patients underwent close monitoring for hypertension, proteinuria, and other adverse effects. The ORR was 44.2% (95% confidence intervals [CI] 30.5–58.7%) and after a median follow-up period of 31 months, median overall survival (OS) was 29.9 months (95% CI 20.3, to not estimable; range 2.4–35.8 months). Another secondary endpoint was time to progression, which was 15.7 months. The 5-year OS rate of this cytokine-refractory mRCC population was 20.6%, as assessed during long-term follow-up [24]. Also, this longer follow-up did not reveal any new toxicity in the patient cohort [24]. Narrower distribution of peak drug concentration on day 1 of cycle 1, higher ORR, and better baseline performance status were characteristics significantly associated with 5-year survival.

Table 1 Summary of phase 2 trials of axitinib

Patients	ORR (%)	TTP/PFS (months)	OS (months)
Cytokine refractory [21]	44.2	15.7	29.9
Sorafenib refractory [22]	22.6	7.4	13.6
Cytokine refractory [23]	50.0	11.0	NR

Table 1 summarizes data from phase 2 axitinib trials, references listed in parenthesis
NR not reported, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *TTP* time to progression

Subsequently, a second phase 2 study of 62 patients was conducted to evaluate response to axitinib in patients who had received prior VEGF therapy with sorafenib [22]. In this single-arm study, dose escalation was permitted if standard 5 mg b.i.d. dosing was tolerated. Additionally, the protocol allowed for dose reduction or interruption for grade 3–4 (severe, disabling, or life-threatening) nonhematologic toxicities (per National Cancer Institute Common Terminology Criteria for Adverse

Events [NCI-CTCAE], version 3.0). A total of 53.2% of patients were able to tolerate dose increases to 7 or 10 mg b.i.d, while 17.7% of patients required dose reductions to ≤5 mg b.i.d. The primary endpoint of ORR was 22.6% (95% CI 12.9–35.0%). With a median follow-up of 22.7 months, median progression-free survival (PFS) was 7.4 months (95% CI 6.7–11.0 months), and median OS was 13.6 months (95% CI 8.4–18.8 months). Interestingly, 80% of the evaluable patients had some degree of tumor shrinkage.

A phase 2 study of axitinib in Japanese patients who were cytokine refractory has also yielded similar results, with an ORR of 50.0%, and median PFS of 11.0 months, which confirms the previously observed efficacy and tolerability in non-Caucasian populations [23].

Phase 3 AXIS Study

The AXIS trial was a pivotal, phase 3, randomized controlled study of 723 patients, which compared two targeted agents in mRCC wherein patients were randomized to receive either axitinib 5 mg b.i.d. or sorafenib 400 mg b.i.d. (standard of care) [25]. The primary endpoint of median PFS was 6.7 months for axitinib versus 4.7 months for sorafenib (hazard ratio [HR] for disease progression or death of 0.665 [95% CI 0.544–0.812], $P < 0.0001$; Fig. 1a) [25]. Median PFS for patients who had previously received cytokine therapy was 12.1 months for axitinib and 6.5 months for sorafenib (HR = 0.464; 95% CI 0.318–0.676; $P < 0.0001$; Fig. 1b). Among patients previously treated with sunitinib, median PFS was 4.8 months for axitinib and 3.4 months for sorafenib (HR = 0.741; 95% CI 0.573–0.958; $P = 0.0107$; Fig. 1c). Secondary endpoints included ORR, OS, and safety and tolerability. ORR was 19.4% (95% Cl 15.4–23.9%) versus 9.4% (95% CI 6.6–12.9%) with axitinib and sorafenib, respectively.

The prolonged PFS with both axitinib and sorafenib in sunitinib-refractory cases, although modest, provides evidence favoring lack of cross-resistance between different VEGFR inhibitors. These data support the use of sequential VEGFR inhibitors, although optimal sequencing to maximize PFS in mRCC is currently the subject of ongoing research [26–29].

Secondary analysis of the AXIS trial has suggested that of the nearly 54% of patients (in both sorafenib and axitinib arms) who had received prior sunitinib, those who had received ≥9 months of front-line VEGFR inhibitor tended to have greater PFS (6.3 months vs. 4.5 months for axitinib; 4.6 vs. 2.9 months for sorafenib), although these data are to be regarded as hypothesis-generating given the retrospective nature and small subsets with overlapping CIs [30]. Upcoming trials of sequential therapy may reflect further on this observation.

In the AXIS trial, patient-reported outcomes were assessed by the Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI) questionnaire, as well as FKSI-Disease Related Symptoms (FKSI-DRS) subscale, at the onset of therapy and then monthly until 28 days after the last drug dose [25]. An analysis of time to deterioration demonstrated 17% reduction in FKSI ($P = 0.014$) and 16% reduction in FKSI-DRS ($P = 0.0203$) with axitinib compared with sorafenib. These data suggest that the benefit in PFS gained with axitinib is accompanied by a delay in symptoms of advanced RCC in the second-line setting.

PHARMACODYNAMICS AND PHARMACOKINETICS

Available as 5 mg and 1 mg tablets, axitinib achieves peak plasma concentration in 3 hours after a high-fat, high-calorie meal, and 2 hours after overnight fasting [31]. According to

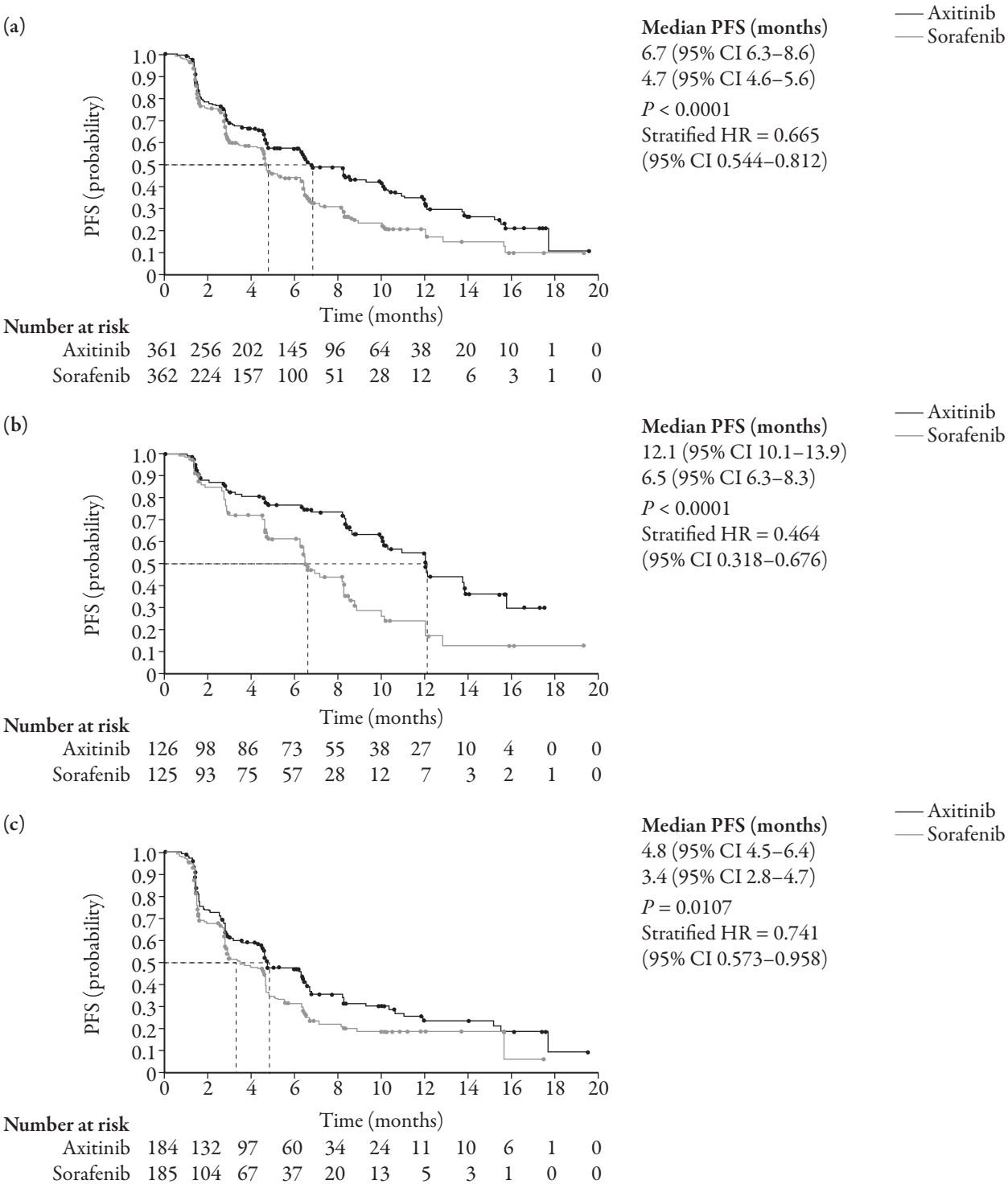

Fig. 1 Kaplan-Meier-estimated median PFS in all patients (**a**), patients previously treated with cytokine-based regimen (**b**), and patients previously treated with sunitinib-based regimen (**c**), who received axitinib or sorafenib as second-line therapy for metastatic renal cell cancer. *Reproduced with permission from Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011;378:1931–9. PFS* progression-free survival, *HR* hazard ratio

manufacturer's guidelines, it may be taken with or without meals [32]. B.i.d. dosing achieves 1.4-fold greater accumulation compared with once-a-day dosing. With a plasma half-life of 2.5–6.1 hours, steady state is achieved within 2–3 days. The drug is primarily metabolized by cytochrome P450 (CYP) 3A4/5, and to a lesser extent by CYP1A2, CYP2C19, and uridine diphosphate glucuronosyltransferase 1 polypeptide A1 (UGT1A1) [33]. Axitinib is an inhibitor of the efflux transporter P-glycoprotein (P-gp) in vitro, but is not expected to inhibit P-gp at therapeutic plasma concentrations. Axitinib is eliminated by hepatobiliary excretion and phase 1 studies have suggested <1% excretion of the drug in urine [17]. Dose modifications are not recommended for patients with mild hepatic impairment (Child-Pugh A) [34]. While axitinib has not been studied in patients with severe hepatic failure (Child-Pugh C), the starting dose should be reduced by 50% in patients with moderate hepatic failure (Child-Pugh B). The incidence of grade 3–4 transaminitis (defined as aspartate transaminase [AST], alanine aminotransferase [ALT] >5–10-times the upper limit of normal) is <1%; however, baseline and periodic monitoring of AST, ALT, and bilirubin are recommended through the course of treatment for all patients. No starting dose adjustments have been recommended in pre-existing mild-to-severe renal impairment, but caution is advised in end-stage renal disease (creatinine clearance <15 mL/min) [32].

Coadministration of axitinib with strong CYP3A4/5 inhibitors (e.g., grapefruit, ketoconazole, itraconazole, clarithromycin, atazanavir) may increase axitinib plasma concentrations. On the other hand, coadministration with strong CYP3A4/5 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, and St. John's Wort) may decrease plasma concentrations [32].

Pharmacodynamic Variability

Investigators recently analyzed single nucleotide polymorphisms (SNPs) in VEGF and related receptors, and their correlation with hypertension and PFS in the phase 3 axitinib AXIS study [35]. Preliminary data suggest that three VEGF-A SNPs revealed potential association between VEGF genotype and PFS. Although these data are preliminary, it is noteworthy that these polymorphisms were not associated with axitinib-related hypertension or diastolic hypertension [35]. Additionally, a meta-analysis of pooled data from 11 axitinib studies has not revealed a significant association linking gene polymorphism for enzymes CYP3A4/5, CYP1A2, CYP2C19, UGT1A1, and P-gp to variations in axitinib pharmacokinetics [36]. Additional investigation into pharmacogenomics as they relate to axitinib efficacy and toxicity is needed.

DOSE ESCALATION

In the AXIS trial, dose escalation of axitinib was permitted based on physician discretion in patients without hypertension (defined as blood pressure ≥150/90 mmHg), absence of toxicities more than grade 2 (by Common Terminology Criteria for Adverse Events [CTCAE] version 3.0), and absence of the use of antihypertensive agents. In patients satisfying these criteria, dose escalation was allowed from 5 to 7 mg b.i.d. after 2 weeks. Additionally, dose escalation was permitted in another 2 weeks to 10 mg b.i.d. in patients who continued to satisfy the above criteria, with additional provision for dose reduction in cases of adverse toxicities and physician discretion used throughout [25].

Results of a secondary analysis did not reveal a significant difference in median PFS among patients who received daily doses of axitinib ≤10 mg compared with patients

receiving higher doses of axitinib, with both groups having better PFS than the sorafenib arm [30]. This result is to be expected on the basis of axitinib pharmacokinetics. That is, patients who tolerated the 5 mg b.i.d. standard starting dose may have subtherapeutic axitinib drug levels. Dose escalation to 7 or 10 mg b.i.d. elevates axitinib drug levels in those patients to above threshold, comparable to patients who do experience hypertension or other toxicity at 5 mg b.i.d. Thus, dose titration with axitinib normalizes blood levels in a subset of patients, allowing them to achieve therapeutic axitinib levels and, thus, an antitumor effect. Given interpatient variability in the ability to achieve therapeutic plasma drug levels, dose escalation of axitinib is critical for optimal administration, as is true for many, if not all oral agents.

Enrollment for a randomized phase 2 study to evaluate efficacy of front-line axitinib with dose titration in 200 treatment-naive patients has been completed [37]. In this study, after 4 weeks of standard dosing (5 mg b.i.d.), eligible patients were randomized to a dose titration arm (standard dose plus escalating doses of axitinib, arm A) versus standard dose and escalating doses of placebo (arm B). Eligibility for dose titration was based on absence of hypertension (>150/90 mmHg), grade 3 or 4 toxicities, prior dose reduction, and use of more than two antihypertensive agents. Patients not meeting randomization criteria for dose titration continued on standard dosing in a third arm (arm C). Preliminary analysis performed in a subpopulation that had pharmacokinetic assessments on day 15 of cycle 1 indicated that patients with drug exposure above the therapeutic threshold (area under the plasma concentration time curve from 0–12 h [AUC_{0-12}] ≥150 ng/mL) on day 15 of cycle 1 had a longer median PFS and higher ORR than those with subtherapeutic exposure (median PFS: 13.9 months vs. 8.3 months; ORR: 59% vs. 48%). In a blinded pooled analysis of the entire enrolled population, ORR in arm C was higher (56.0%; 95% CI 45.2–66.4%) compared with arms A+B (40.2%; 95% CI 31.0–49.9). These data suggest that response rates and PFS more likely depend on achievement of therapeutic concentration of axitinib, rather than specific drug dosage. This lends support to consideration of dose escalation to improve treatment response, by optimization of plasma drug levels. The unblinding of this study and comparison of patients eligible for dose titration who underwent dose escalation versus patients who did not, will provide more definitive insight into the clinical utility of dose escalation.

Dose Titration

Currently, the recommended oral starting dose of axitinib is 5 mg b.i.d. Periodic monitoring of blood pressure is recommended. In patients who do not develop dose-limiting toxicity (grade 3 or 4), are normotensive, and are not receiving antihypertensive agents, uptitration to 7 mg b.i.d. 2 weeks after initiation is suggested. Using the same principle, the dose can be increased to a maximum of 10 mg b.i.d. In patients who require dose reduction because of adverse effects, a decrease to 3 mg b.i.d. is recommended. Further dose reduction to 2 mg b.i.d. may be necessary in some cases.

TOXICITIES AND THEIR MANAGEMENT

Based on results of the AXIS trial, common adverse effects of axitinib that have been observed in over 30% of patients (all grade toxicities) include diarrhea, hypertension, fatigue, nausea, lack of appetite (anorexia), and dysphonia [25]. Among laboratory abnormalities,

anemia, hypothyroidism, lymphopenia, and hypocalcemia were commonly seen. Less common side effects included bleeding, thromboembolism, and proteinuria. Table 2 [25] summarizes the various grades of toxicities observed in the phase 3 study. The decreased incidence of myelosuppression, hand-foot syndrome (palmar-plantar erythrodysesthesia),

Table 2 Common treatment-emergent all-causality adverse events in the phase 3 AXIS trial

Treatment-emergent events	Axitinib (*n* = 359)		Sorafenib (*n* = 355)	
	All grades	≥Grade 3	All grades	≥Grade 3
Adverse events				
Diarrhea	197 (55)	38 (11)	189 (53)	26 (7)
Hypertension	145 (40)	56 (16)	103 (29)	39 (11)
Fatigue	140 (39)	41 (11)	112 (32)	18 (5)
Decreased appetite	123 (34)	18 (5)	101 (29)	13 (4)
Nausea	116 (32)	9 (3)	77 (22)	4 (1)
Dysphonia	111 (31)	0	48 (14)	0
Palmar-plantar erythrodysesthesia	98 (27)	18 (5)	181 (51)	57 (16)
Weight decreased	89 (25)	8 (2)	74 (21)	5 (1)
Vomiting	85 (24)	12 (3)	61 (17)	3 (1)
Asthenia	74 (21)	19 (5)	50 (14)	9 (3)
Constipation	73 (20)	4 (1)	72 (20)	3 (1)
Hypothyroidism	69 (19)	1 (<1)	29 (8)	0
Cough	55 (15)	3 (1)	59 (17)	2 (1)
Mucosal inflammation	55 (15)	5 (1)	44 (12)	2 (1)
Arthralgia	54 (15)	5 (1)	39 (11)	5 (1)
Stomatitis	54 (15)	5 (1)	44 (12)	1 (<1)
Rash	45 (13)	1 (<1)	112 (32)	14 (4)
Alopecia	14 (4)	0	115 (32)	0
Laboratory abnormalities[a]				
Anemia	113/320 (35)	1/320 (<1)	165/316 (52)	12/316 (4)
Hemoglobin elevation	31/320 (10)	NA	3/316 (1)	NA
Neutropenia	19/316 (6)	2/316 (1)	26/308 (8)	2/308 (1)
Thrombocytopenia	48/312 (15)	1/312 (<1)	44/310 (14)	0
Lymphopenia	106/317 (33)	10/317 (3)	111/309 (36)	11/309 (4)
Creatinine elevation	185/336 (55)	0	131/318 (41)	1/318 (<1)
Hypophosphatemia	43/336 (13)	6/336 (2)	158/318 (50)	51/318 (16)
Hypercalcemia	19/336 (6)	0	5/319 (2)	0
Hypocalcemia	132/336 (39)	4/336 (1)	188/319 (59)	5/319 (2)
Lipase elevation	91/338 (27)	16/338 (5)	148/319 (46)	47/319 (15)

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Data are *n* (%)

NA not available

[a] Denominator for each laboratory abnormality differed depending on the availability of baseline and at least one on-study test result

and cutaneous toxicities with axitinib compared with other VEGFR inhibitors is a potential advantage of axitinib.

The most important component of side-effect management is patient education prior to treatment initiation. The clinician's knowledge of common side effects provides the basis for focused education. Patient education should include necessary information regarding the treatment plan, dosing, and potential drug–drug interactions (Table 3) [38].

Hypertension should be controlled prior to the initiation of therapy. Home blood pressure assessments should be individualized based on the patient's medical history, concomitant medications, and drug therapy. Patients with a history of hypertension, cardiac co-morbidities, renal dysfunction, or diabetes should be closely monitored for treatment-induced hypertension [39]. Early awareness of changes in home blood pressure assessments allows the clinician to begin or adjust antihypertensive medications, improve control of hypertension, and minimize the patient's risk of developing hypertension-related toxicity.

Management of axitinib-associated gastrointestinal side effects includes dietary and medication interventions. Information about dietary management of diarrhea should be given to the patient prior to the initiation of therapy, including consumption of bananas and rice, and the avoidance of spicy foods. Pharmacologic interventions include loperamide, diphenoxylate hydrochloride/atropine sulfate, tincture of opium, probiotics, and psyllium fiber supplements [40]. Avoiding caffeinated beverages and increasing fluid intake can decrease the potential for diarrhea, dehydration, and renal dysfunction. Frequent meals, increasing calorie intake, nutritional supplements, and consultation with a nutritionist can minimize the negative impact of anorexia.

Hand-foot syndrome is a class effect of VEGF-TKIs, and requires ongoing assessment and management to control the extent and severity of this adverse event. Assessment of skin condition and noting the presence of calluses or structural abnormalities that increase pressure on bony prominences should be done at baseline, at each clinic visit, and discussed during phone assessments thereafter. Instructions regarding proactive skin care and supportive footwear should be provided at baseline, with ongoing evaluation and adjustment of interventions throughout treatment. The "3C" approach to management of hand-foot syndrome includes controlling calluses, comforting with cushions, and covering with creams, and provides an

Table 3 Instructions to include in patient information packet for axitinib

- Treatment information regarding axitinib drug formulation and dosing.
- Information regarding possible food and drug interactions, and other precautions to consider with axitinib therapy.
- Possible side effects, prevention, and early management strategies. This should include a discussion regarding which side effects may be prevented or less severe with prophylactic management (i.e., initiation of oral and skin care regimens prior to initiation of treatment).
- Contact information for their nurse, oncologist, and other healthcare team members, including who (and how) to contact when the office is closed. Emphasize the importance of early communication with the nurse/oncologist as side effects develop.
- Specific instructions regarding home monitoring of blood pressure.
- Daily log to record the day, dose, and time of drug administration, along with space to document side effects and blood pressure measurements.

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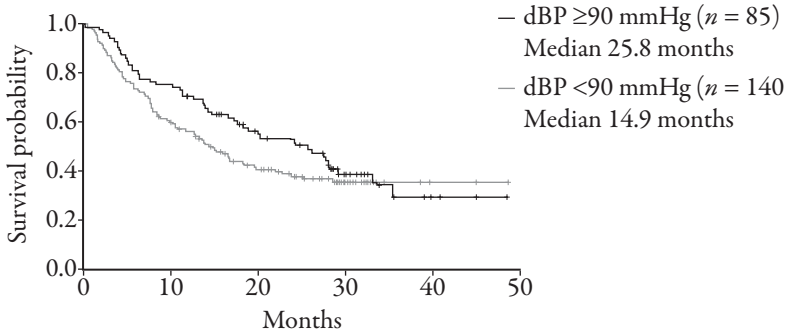
easy-to-remember method for patient education and intervention strategies [41, 42].

Treatment modification including interruption and dose modification may be required in spite of effective patient education, proactive strategies, and frequent and ongoing communication to adjust interventions for drug-related side effects. Interventions directed at fatigue include energy conservation, activity enhancement, psychosocial and nutritional interventions, and psychostimulants after ruling out other causes of fatigue [43]. Hypothyroidism is also associated with the increased incidence of fatigue, emphasizing the importance of obtaining baseline and ongoing thyroid function testing [38, 43]. Hypothyroidism with VEGFR inhibitors may result from inhibition of angiogenesis around the thyroid gland. Thus, periodic monitoring of thyroid function is recommended.

Hypertension as a Biomarker

Hypertension is a significant adverse effect of axitinib, with reported incidence (all grades included) of approximately 40–50% [25]. Hypertension as a class effect of VEGF-TKIs may be secondary to reduced production of the vasodilator, nitric oxide, which is a VEGFR-mediated phenomenon [44]. Thus, hypertension may be a surrogate marker of "on-target" activity of axitinib. This was revealed in a retrospective study of five, phase 2 trials of single-agent axitinib [45], wherein diastolic hypertension (defined as diastolic blood pressure ≥90 mmHg) was associated with a lower relative risk of disease progression (HR = 0.76; 95% CI 0.54–1.06; P = 0.107]. Furthermore, in an 8-week landmark analysis, diastolic hypertension was associated with improved OS (Fig. 2) [45]. In this 8-week analysis, median PFS for the two mRCC studies was noted to be significantly higher in patients with diastolic hypertension: 16.5 versus 6.4 months (HR = 0.53; 95% CI 0.31–0.9; P = 0.019). This suggests that diastolic hypertension correlates with drug efficacy [45].

Importantly, treatment of hypertension itself is not expected to affect antitumor activity [15]; thus, axitinib-induced hypertension should be aggressively managed with standard antihypertensives. Additionally, preliminary subset analysis of the phase 2 front-line study of axitinib with dose escalation has suggested that patients with mean increases of diastolic blood



Patients at risk (*n*)					
dBP <90 mmHg	140	83	49	18	2
dBP ≥90 mmHg	85	64	39	17	3

Fig. 2 Overall survival in patients with and without dBP ≥90 mmHg with landmark analysis at 8 weeks. *Reproduced with permission from Rini BI, Schiller JH, Fruehauf JP, et al. Diastolic blood pressure as a biomarker of axitinib efficacy in solid tumors. Clin Cancer Res. 2011;17:3841–9. dBP* diastolic blood pressure

pressure at , day 15 of cycle 1 compared with baseline (ΔdBP) ≥15 mmHg have a higher ORR than ΔdBP <15 mmHg (61% vs. 53%) [37].

CONCLUSION

In conclusion, axitinib has expanded available options for mRCC patients. Selective inhibition of the VEGFR-1, 2, and 3 at clinically applicable concentrations and biochemical potency against VEGFR contribute to its clinical efficacy. Prolonged median PFS is achievable compared with an active comparator in refractory patients, and is currently being evaluated in the front-line setting in mRCC. Analysis of patient-reported outcomes also suggests a delay in symptoms in patients with advanced RCC. Overall, the major dose-limiting adverse effects of axitinib include hypertension, diarrhea, and fatigue. Importantly, hypertension may be a useful biomarker of drug efficacy. Dose escalation is of considerable interest and is undergoing further evaluation in phase 2 studies. Ongoing phase 3 studies are also assessing the role of axitinib in the front-line setting [46], as well as adjuvant treatment in high-risk patients [47].

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