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REVIEW

Tyrosine Kinase Inhibitors in the Treatment of Advanced Renal Cell Carcinoma: Focus on Pazopanib

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Abstract: Advances in our understanding of renal cancer biology have led to a new treatment paradigm in renal cancer. Tyrosine kinase inhibitors (TKI), that target the intracellular kinase domain of the VEGF receptor, have become established as the most successful class of agent in this disease. Three TKIs are currently approved for use in patients with advanced disease. Newer, more potent inhibitors have reached phase III clinical testing, meaning others are likely to follow. In 2009, pazopanib became the most recent TKI to receive FDA approval. This review sets out to discuss the key opportunities and challenges associated with TKI use in RCC, focusing particularly on pazopanib. We also review the current place of pazopanib in the management of patients with advanced disease, in what is a rapidly evolving therapeutic landscape.

Keywords: pazopanib, tyrosine kinase inhibitor, renal cell carcinoma, VEGF

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Introduction

Renal cancer

Renal cell carcinoma (RCC) accounts for 2%–3% of all adult malignancies, with an estimated 270,000 new cases and 116,000 deaths worldwide each year.[1] Incidence rates vary substantially across the world, with higher rates observed in North America and Europe in comparison to Asia and Africa. After over two decades of increasing rates, RCC worldwide incidence trends show signs of plateauing or decreasing in recent years.[2] The most common histological subtype of RCC is the conventional or clear cell type accounting for 70%–80% of cases. The rest are composed of papillary, chromophobe, and collecting duct tumors although accurate histological distinction is not always possible.[3]

Central to the biology of sporadic clear cell RCC is loss of function of the Von Hippel Lindau (VHL) tumor suppressor gene, located on chromosome 3p. Recent comprehensive genetic studies suggest very high rates (>95%) of VHL involvement through mutation, methylation and loss of heterozygosity analysis such that VHL loss of function may provide a molecular basis for classification as clear cell RCC.[4] The VHL gene products function in the hypoxia inducible pathway, forming a multiprotein complex that principally functions to ubiquitinate hypoxia inducible factor-alpha (HIF-α) leading to its proteasomal degradation.

HIF is a heterodimeric transcription factor consisting of an unstable α subunit and a stable beta (β) subunit. Under low oxygen conditions or in cells lacking pVHL, HIF-α accumulates, binds to HIF-β, and transcriptionally activates genes whose promoters contain hypoxia-response elements. Up to 100 HIF-responsive genes have been described, many of which are involved in the adaptation to acute or chronic hypoxia.[5] These include glucose transporters (eg, GLUT1) and growth factors such as transforming growth factor-α, as well as the highly pro-angiogenic factors vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). RCCs are characterised as being highly vascular tumors, driven by VEGF-dependent angiogenesis. Angiogenesis, the growth of new vessels from pre-existing vasculature, is a critical step in tumor progression.[6] Inhibition of the VEGF pathway has proven a highly effective therapeutic strategy in RCC, improving the outlook for patients with advanced disease. This may be achieved via monoclonal antibodies targeted to bind VEGF (eg, bevacizumab) or through intracellular inhibition of VEGF signalling through the use of small molecule tyrosine-kinase inhibitors (TKIs) that target the intracellular kinase domains of the VEGF receptors (VEGFR1-3). Receptor tyrosine kinases are essential for the transduction of extracellular signals into the cell. A receptor tyrosine kinase monomer consists of an N-terminal extracellular ligand-binding domain, a transmembrane domain, and a C-terminal intracellular domain with tyrosine kinase activity. The kinase domain has a bi-lobar structure, with an ATP-binding cleft located between the N- and C-terminal lobes.[7]

Tyrosine kinase inhibitors

Since the approval six years ago of the first TKI for RCC, these agents have gone on to become the most successful class of drug used in the treatment of this disease. They are classed as anti-angiogenic agents, thought primarily to function by inhibiting tumor endothelial growth and survival signalling. Three TKIs are currently approved in the US and Europe: sorafenib (Nexavar; Bayer Pharmaceuticals), sunitinib (Sutent; Pfizer Inc) and pazopanib (Votrient; GlaxoSmithKline). Two others, axitinib (AG-013736; Pfizer Inc) and tivozanib (AV-951; Aveo Pharmaceuticals), have reached phase III clinical testing. A summary of these agents is presented in Table 1.

Sunitinib was granted Food and Drug Administration (FDA) approval in January 2006 and still represents the current standard of care in the first line metastatic setting. In a landmark randomized phase III study, sunitinib doubled median progression-free survival (PFS) in comparison to interferon-α (the then standard) from 5 months to 11 months amongst 750 patients with metastatic RCC (mRCC) (Hazard Ratio (HR) 0.42 (95% confidence interval, 0.32 to 0.54; $P < 0.001$), with median overall survival (OS) of >2 years.[8,9] Sorafenib, FDA approved in October 2005, improved PFS from 2.8 months to 5.5 months versus placebo ($P < 0.01$) amongst 903 cytokine refractory patients.[10] From these initial, and subsequent, studies, however, it became clear that the TKIs presented their own set of challenges. Firstly, the TKIs were associated with a number of common toxicities. Secondly, resistance was observed, either intrinsically or otherwise invariably acquired. Thirdly, there was a

Table 1. TKIs approved or in phase III testing for use in RCC.

	PFS (months)		Dose	Schedule
	Treatment naive	Cytokine refractory		
Pazopanib[27]	11.1	7.4	800 mg od	Continuous
Sunitinib[8,59]	11.0	8.3	50 mg od	4 wks on/2 wks off
Sorafenib[10,60]	5.7	5.5	400 mg bd	Continuous
Axitinib[57]	NA	12.1	5 mg bd	Continuous
Tivozanib[58]	14.3	15.8	1.5 mg od	Continuous

Abbreviations: NA, Not available; PFS, Progression Free Survival.

lack of predictive biomarkers of response. Fourthly, assessment of response by standard Response Evaluation Criteria In Solid Tumors (RECIST) was recognised as inadequate. And finally, what, if any, sequence in which to use these drugs was unclear.

Common to all currently used TKIs is that they are multi-targeted agents, inhibiting a number of receptor kinases including PDGFR α and β, stem cell factor receptor (KIT), RET and FMS-like tyrosine kinase-3 (Flt-3) in addition to VEGFRs, with varying potency.[11] This lack of specificity brings with it a number of common side-effects, often termed 'off-target' effects, including hypothyroidism, hand-foot syndrome, diarrhea, stomatitis and anorexia. Others, such as hypertension and lethargy, may in fact represent 'on-target' toxicities. Thus many patients require dose reductions (or stop therapy altogether), which may negatively impact on both quality of life and survival.[12] This has led to the introduction of a new generation of TKIs such as axitinib and tivozanib that have a much higher potency and selectivity for VEGFRs which, it is hoped, will lead to better tolerated and more efficacious therapy.

No matter how potently the VEGF pathway is blocked, resistance to TKIs invariably develops, typically within months of commencing therapy. The underlying mechanisms behind this are poorly understood. Resistance is likely to be a process that involves complex tumor-stromal interactions. A number of mechanisms have been proposed which remain under investigation.[13] Possibilities include the increased production of alternative pro-angiogenic growth factors,[14] acquired tumor cell resistance[15] and inflammatory cell infiltration.[16] The observation of responses following sunitinib re-challenge[17] or with sequential TKI use[18] are intriguing and further raise the possibility that such mechanisms are reversible. Unlike other tumor types treated with targeted therapies, there remains a lack of biomarkers that allow prediction of response to TKIs amongst individual patients with RCC. Such markers are important to avoid unnecessary toxicity and potentially carry important health economic benefits.

In October 2009, pazopanib became the third and most recently approved TKI for use in advanced RCC by the FDA. In the UK, the National Institute for Clinical Excellence (NICE) approved its use in the first line setting for patients with metastatic RCC and Eastern Cooperative Oncology Group (ECOG) performance status 0–1. This review will focus on the key clinical data supporting the use of this drug and attempt to interpret this data in the context of what is a rapidly evolving therapeutic landscape.

Mechanism of Action, Metabolism and Pharmacokinetic Profile

Pazopanib hydrochloride is an orally bioavailable, multi-targeted TKI that inhibits the function of multiple receptor kinases including VEGFR1-3, PDGFRα/β, fibroblast growth factor receptor 1, 3 and 4 (FGFR), KIT, and RET. A comparison of TKIs currently used in RCC, their kinase targets and inhibitory concentrations has recently been reported by Cowey et al.[19] Such comparisons of relative potency, as measured by IC_{50} against VEGFR2, suggest that pazopanib (30 nmol) is comparable to sunitinib (10 nmol) and sorafenib (90 nmol) in this regard. However pazopanib may have a narrower target range, with a quicker drop-off in terms of off-target inhibition.[19]

Pazopanib is taken on a continuous cycle at a dose of 800 mg daily, based on Phase I data.[20] Its half-life is approximately 30 hours and time to peak plasma concentration is between 2 and 4 hours.[20] It is metabolised by cytochrome P_{450} 3A4 (CYP3A4) and hence

patients must avoid concomitant use with strong inhibitors and inducers of this enzyme. Elimination is primarily via feces with renal elimination accounting for <4% of the administered dose.[21]

Crushing tablets or taking oral suspension increases plasma concentration approximately 100% and 29% respectively, and decreased time to achieve maximum plasma concentration (by approximately 2 h and 1 h respectively), indicating increased rate and extent of oral absorption relative to whole-tablet administration.[22] A similar effect is observed following administration of pazopanib with low- and high-fat meals, such that the drug should ideally be taken at least one before or two hours after a meal.[21,23]

Clinical Efficacy

The phase I[20] and II[24] data for pazopanib have been summarized elsewhere.[25,26] The phase III study (VEG105912) of pazopanib that led to its approval was a placebo-controlled, randomized, double-blind, multi-center study.[27] Patients were required to have clear-cell or predominantly clear cell histology, ECOG PS ≤1 and could be either treatment naïve or have progressed on prior cytokine therapy. Patients were randomized 2:1 to receive either pazopanib 800 mg od or placebo. Cross-over at progression was allowed, such that patients on placebo could subsequently receive active drug (extension trial, VEG107769). The primary end-point of the study was PFS.

435 patients were enrolled, with 290 and 145 patients in the pazopanib and placebo arms respectively. The two arms were well matched, with 53% and 54% patients being treatment naïve amongst pazopanib and placebo treated cohorts. 94% of patients were good or intermediate prognosis as per Memorial Sloan Kettering Cancer Center (MSKCC) criteria.

Pazopanib significantly prolonged PFS in comparison to placebo (median PFS 9.2 months versus 4.2 months; HR 0.46; $P < 0.0001$) amongst all patients. The difference was more pronounced amongst the subset of treatment naïve patients (PFS 11.1 months versus 2.8 months; HR 0.40; $P < 0.0001$) than those pre-treated with cytokines (PFS 7.4 versus 4.2 months; HR 0.54; $P < 0.001$). Response rate (by independent review) was 32% versus 4% amongst treatment naïve patients with a median duration of 58.7 weeks. Final OS data have since been presented and showed a median OS of 22.9 vs. 20.5 months in the pazopanib and placebo arms respectively (HR: 0.91; $P = 0.224$). However, OS was confounded by extensive crossover of placebo patients to pazopanib and other therapies. More placebo than pazopanib patients received subsequent treatment (66% vs. 30%, respectively) with 54% of placebo patients crossing to pazopanib, some as early as week 6. Two independent analyses to adjust for crossover were conducted, IPCW (Inverse Probability of Censoring Weighted) and RPSFT (Rank Preserving Structural Failure Time) suggest an OS benefit with pazopanib (HR 0.5; $P = 0.002$ by IPCW and HR 0.43; $P = 0.172$ by RPFST).[28]

Health-related quality of life (HRQoL) was also examined as part of the study, reporting no evidence of a clinically important difference between pazopanib and placebo treated patients at each assessment timepoint. In a subsequent post hoc analysis, time to HRQoL deterioration and association of changes in HRQoL with response were analysed. No significant difference was found in terms of time to deterioration of HRQoL. However, patients with complete response or partial response experienced significantly less HRQoL deterioration than those with progressive disease ($P < 0.001$ and $P = 0.0024$ respectively).[29]

Patients with polymorphisms in genes that increase CYP3A4 expression, and therefore potentially lower plasma drug levels, have a lower response rate to pazopanib[30] and increased plasma concentrations of TKIs have been associated with better outcome in patients with metastatic RCC.[31] Amongst 225 pazopanib treated patients, those who achieved a trough plasma level of >20.6 μg/ml after 4 weeks of treatment had a better response rate (45% versus 18%) and PFS (49.4 weeks versus 20.3 weeks; $P = 0.004$) than those <20.6 μg/ml.[32]

Data regarding the efficacy of pazopanib after prior targeted therapy for advanced RCC has also recently been reported. In a phase II study, 44 patients with mRCC who had progressed on either sunitinib (n = 32) or bevacizumab (n = 12) received pazopanib second-line. Overall response rate was 20%, with a median PFS of 9.2 months.[33] In a retrospective single-institution series involving 88 patients, second-line pazopanib demonstrated activity, with a response rate of 42% and 18% amongst patients who had failed 1 and >1 prior targeted therapy respectively ($P = 0.02$).

Median time to progression was 71 days. The patients were heavily pre-treated (median number of prior targeted agents was 2, range 1–5) with 58% of patients having failed both TKI and mTOR based therapies. Almost one half of patients also had poor-risk disease by MSKCC criteria.[34]

Safety

Within the phase III study of pazopanib, 14% of all patients stopped drug due to adverse events (AE) (12% amongst treatment naïve patients). Comparative discontinuation rates due to AEs are shown for all TKIs in Table 2, where available. The most commonly reported AEs were diarrhea, hypertension, nausea, anorexia and vomiting. The most common grade 3/4 AEs were hypertension (4%), diarrhea (3%) and asthenia (3%). The incidence of hemorrhagic events was 13% in the pazopanib arm compared to 5% in the placebo arm. 1% of patients had fatal AEs attributable to pazopanib as assessed by the investigator.

Recently presented data suggests that the frequency of some, but not all, toxicities increase as plasma concentration of pazopanib increases. When considered as quartiles based on trough levels of pazopanib, incidence of hand foot syndrome (all grades) rose from 0% (Q1) to 24% (Q4). Similarly, diarrhea increased from 24% to 67% and hypertension from 58% to 78%. No significant difference was noted in incidence of fatigue, nausea and vomiting. The data are revealing and suggest dose reductions may be effective for certain side-effects, but for others, such as fatigue, may have minimal impact.[35]

The main toxicities associated with the TKIs are summarised in Table 3. Clearly, comparisons across clinical trials must be made with caution but, to date, only one head-to-head trial has been reported.[56] It is evident that rates of hypertension and diarrhea are similar across all agents, with the exception of tivozanib that appears to cause less diarrhea. Rates of fatigue appear to be lower with pazopanib than other first-generation TKIs. Part of the explanation for this may lie in the fact that pazopanib is associated with low rates of thyroid dysfunction. Agents such as sunitinib have a reported incidence of between 53%–85%.[36,37] In comparison, amongst 578 RCC patients treated with pazopanib within phase II and III studies, hypo- and hyperthyroidism were diagnosed in just 3% and 1% of patients respectively.[38]

In addition, it is evident that the incidence of hand-foot syndrome in pazopanib treated patients is notably lower than that seen with sunitnib, sorafenib and axitinib. Amongst >900 patients treated with pazopanib 800 mg daily within 10 prospective clinical cancer trials, the incidence of all-grade and high-grade hand-foot syndrome was 4.5% and 1.5% respectively. Interestingly, the incidence of all-grade hand-foot syndrome was significantly higher in patients with RCC as compared to patients with non-renal malignancies (7.8% vs. 2.4%, P value = 0.015).[39]

Pazopanib, like other TKIs, is associated with hepatotoxicity. 18% of patients in the phase III study had an elevation in alanine transaminase (ALT) ≥3x the upper limit of normal. Grade 3/4 elevation of ALT, AST and bilirubin occurred in 12%, 7% and 3% of patients respectively. Concurrent elevation of both ALT and bilirubin is rare (<1%) but can lead to fatal hepatotoxicity. Patients' liver function tests must therefore be monitored closely during treatment with dose reduction/interruption if transaminitis occurs. The underlying mechanism of pazopanib induced hepatotoxicity remains unclear. In the meantime, efforts have focused on identifying patients predisposed to hepatic dysfunction. Xu and colleagues examined 6852 polymorphisms in 282 candidate genes amongst 115 pazopanib-treated white patients with RCC. Polymorphisms in the hemochromatosis gene were found to be significantly associated with elevations of ALT, with the rs2858996 TT genotype having an odds ratio for ALT ≥ 3x the upper limit of normal of 39.7 compared to other genotypes.[40] A frequent association

Table 2. Discontinuation rates due to AEs.

Discontinuation due to adverse events (%)	Pazopanib[27]	Sunitinib[8,59]	Sorafenib[60]	Axitinib[57]
Prior cytokine	19	11	NS	4*
Treatment naïve	12	19	11	NA

Note: *Includes prior anti-VEGF treatment.
Abbreviations: NS, Not stated; NA, Not available.

Table 3. Toxicity profile of TKIs (%; all grades).

Setting	Pazopanib[27]	Sunitinib[8]	Sorafenib[10]	Axitinib[57]	Tivozanib[58]
	First/Second-line	First-line	Second-line	Second-line	First/Second-line
Hypertension	40	30	19.5	40	45
Diarrhea	52	61	55	55	12
Anorexia	22	34	22	<25	5
Fatigue	19	54	34	39	8
Hand-foot syndrome	8[39]	29	56	27	4
Stomatitis	–	30	NS	9	4
Nausea	26	52	17	32	NA
Vomiting	21	31	NS	24	NA

Abbreviations: NA, Not available; NS, Not stated.

between pazopanib-induced hyperbilirubinaemia and Gilbert's syndrome UGTIAI polymorphism has also been reported, suggesting that in patients with isolated rises in bilirubin, some may represent benign manifestation of Gilbert's syndrome.[41]

Patient Selection and Monitoring Response

Response and toxicity to pazopanib, and other TKIs, remains unpredictable in individual patients. There are currently no validated markers to allow selection of patients destined to gain maximal clinical benefit. At a clinical level, models that determine prognosis have been validated in the TKI era but such nomograms do not predict for response.[42] VHL status and circulating levels of angiogenesis-related factors such as VEGF have proven unhelpful.[43,44] This therefore remains an active and ongoing area of research in RCC.

Translational studies as part of large clinical trials are important in this regard. Amongst the 585 patients who received pazopanib within the phase II and III studies of this drug, 397 (68%) consented to a sample of blood being taken for germline analysis. These samples have now been analysed, evaluating 27 polymorphisms amongst 13 genes, including those related to metabolism (CYP3A4/5), transport (ABCB1) and angiogenesis (VEGFA/IL-8/FGF2). Two interleukin-8 (IL-8) polymorphisms (276TT/-251AA), linked to increased gene expression, were associated with a significantly shorter median PFS (27 weeks) than those carrying the wild-type genotype (48 weeks) (HR 1.8; $P = 0.01$). A variant of the HIF1 A genotype was similarly correlated with shorter PFS. Importantly, these correlations were not observed in placebo treated patients, suggesting that these markers may indeed be predictive rather than simply prognostic. IL-8 has been identified as a potential driver of resistance to TKIs at both a pre-clinical and clinical level,[16,45] making the results highly biologically relevant.[30]

Plasma samples from pazopanib and placebo treated patients within the phase III study of pazopanib have also been analysed for levels of cytokines and angiogenesis factors including HGF, IL-6, IL-8, TIMP-1, VEGF, E-Selectin and OPN correlated with outcome. 344 patient samples were examined. Higher levels of IL-8 ($P < 0.006$), HGF ($P < 0.01$), OPN ($P < 0.001$) and TIMP-1 ($P < 0.006$) were associated with shorter PFS amongst pazopanib treated patients. However, with the exception of IL-6, a similar correlation was found amongst placebo treated patients. Thus the majority of markers appear to be prognostic whilst baseline serum IL-6 levels may predict for PFS amongst pazopanib treated patients.[46]

It is intriguing that certain toxicities such as hypertension may serve as surrogate biomarkers of response to TKIs. In a retrospective analysis of >500 patients treated with sunitinib, hypertension (HTN) (defined as systolic blood pressure (SBP) >140 mmHg or diastolic BP (DBP) of >90 mmHg was significantly associated with response rate and survival. Amongst patients with HTN defined by SBP, objective response rate and OS were 54.8% and 30.9 months respectively vs. 8.7% and 7.2 months in patients without HTN ($P < 0.001$).[47] Prospective studies are now planned that will titrate dose of TKI until development of hypertension, to determine whether this improves outcome.[48] Hypothyroidism and hand-foot syndrome (certainly the latter of which would be considered an 'off-target' effect) have also been correlated

with outcome in sunitinib treated patients.[36,49] Their low incidence is unlikely to render them useful in pazopanib treated patients however.

Accurately determining whether patients are deriving benefit from potentially toxic therapy in a timely manner is important for patients and future study design. RECIST has been the standard method of treatment evaluation for solid tumors since their introduction in 2000. Whilst validated in the setting of conventional chemotherapeutic agents, their applicability to assessing and monitoring response in the targeted era has been questioned. Marked improvements in survival associated with the TKIs have not been mirrored by high response rates as per RECIST criteria (sunitinib 31%[8]; pazopanib 30%[27]). It may be more relevant to examine other parameters such as arterial phase density, morphology and size in combination in this setting.[50–52] Studies to date have been small and retrospective and evaluation of these criteria in larger numbers in a prospective manner is required.

Place in Therapy

Treatment options for patients with mRCC have burgeoned in recent years. Three TKIs are currently approved. Application for a fourth, axitinib, has been submitted by Pfizer to both the FDA and European Medicines Agency (EMA) for use in second-line therapy. A fifth, tivozanib, is in phase III testing. A sixth, cediranib, is in phase II second-line studies. Bevacizumab plus interferon is another approved option in first-line therapy, as well as the mTOR inhibitor temsirolimus in patients with poor risk disease. In the second line setting, after anti-VEGF therapy failure, everolimus (another mTOR inhibitor) is the only agent currently approved.

Amongst these agents, sunitinib has emerged as the standard of care and by far the most widely used agent in the first-line setting.[53] This is based on the fact that sunitinib demonstrated superiority over interferon-α, the previous standard of care, in a phase III randomised trial.[8] Such a principle guides modern oncological practice. A head to head randomized phase III trial of sunitinib versus pazopanib (COMPARZ) has recently completed recruitment and the results are eagerly awaited. In the meantime, based on currently available data, should pazopanib be considered as an alternative or indeed preferential first-line option?

Comparisons of PFS (Table 1) suggest both sunitinib and pazopanib to be equally efficacious. If true, then toxicity becomes paramount in determining choice of drug. With seemingly lower rates of hand-foot syndrome, stomatitis, hypothyroidism and fatigue associated with pazopanib, there is certainly a case to be made for its first-line use. Indeed both the National Comprehensive Cancer Network (NCCN) and the European Association of Urology (EAU) guidelines recommend pazopanib as a first-line option alongside sunitinib.[54] But extrapolating data in this manner is not always reliable. Are the two drugs really equally efficacious? And is the toxicity profile of pazopanib favorable? Or just different? There are those that argue that in the absence of phase III data demonstrating superiority of pazopanib over sunitinib, there is no justification for its use at present.[55] Our current approach is to use sunitinib as first-line therapy, reserving pazopanib for those patients intolerant of the former for whatever reason.

The situation is no clearer for pazopanib in the second-line setting. The question of what to use post-cytokine failure has become largely irrelevant. And whilst pazopanib has demonstrated efficacy in such patients, so too have sorafenib and axitinib in phase III trials. The key question is what to do in patients following anti-VEGF based therapy. Everolimus is the current standard of care in this setting, demonstrating an improvement in PFS from 1.9 months (placebo) to 4.9 months ($P < 0.001$) amongst 416 mRCC patients who had received one or two prior lines of treatment.[56] Axitinib has recently shown superiority to sorafenib in a phase III second-line study involving 723 patients pre-treated with one line of therapy including cytokines, bevacizumab/interferon, temsirolimus or sunitinib, increasing PFS from 4.7 to 6.7 months ($P < 0.0001$). The benefit was not significant however amongst the subset of patients pre-treated with sunitinib (3.4 vs. 4.8 months; $P = 0.1$).[57] No equivalent trial data exists for pazopanib, which would now be required to show superiority over everolimus and/or axitinib. Nevertheless, the NCCN include pazopanib as a second-line option following TKI failure, since TKI sequencing has been associated with response.[18]

Future Studies

Pazopanib is currently the subject of a number of trials in renal cancer patients that are either planned or

on going. In the neoadjuvant setting, a phase II study is currently recruiting, in which patients will receive pazopanib for up to 18 weeks prior to surgery, the primary endpoint being rate of partial nephrectomy (NCT01158521). In the adjuvant setting, a randomized phase III trial is currently recruiting, randomizing patients between one year of pazopanib versus placebo (NCT01235962). An important question is whether alternating treatment between two classes of drug can postpone or prevent drug resistance. To answer this, a randomized phase II study exploring the efficacy and feasibility of upfront bi-monthly rotations between everolimus and pazopanib in patients with mRCC is planned (NCT01408004). A second study, that is currently recruiting, will compare 6 different 2-drug "sequences" of everolimus, bevacizumab, or pazopanib (NCT01217931). In the first line metastatic setting, a phase II study will compare pazopanib against temsirolimus in poor risk patients (NCT01392183). Second-line studies after prior VEGF therapy include a study involving patients following any one prior VEGF-TKI (NCT01157091). Finally, early phase studies are currently recruiting patients to examine the safety of using pazopanib in combination with bevacizumab (NCT01202032) (NCT00992121) and everolimus (NCT01184326).

Conclusions

Pazopanib joins a growing number of agents with activity against RCC. Published data demonstrate its superiority over placebo in treatment naïve and cytokine-refractory patients. PFS appears equivalent and safety profile favorable in comparison to the current standard of care, sunitinib. However, results from the phase III COMPARZ study comparing these agents are still awaited. In the meantime, the place of pazopanib in the management of patients remains the subject of debate.

The emergence of second-generation TKIs makes the future for pazopanib less certain still. Tivozanib, for example, shows promising activity and is currently in phase III trial testing against sorafenib in treatment naïve or cytokine refractory patients with advanced clear cell RCC (NCT01030783). This choice of comparator, rather than sunitinib, will, however, make the results difficult to interpret in terms of current clinical practice.

A key issue for all TKIs is the invariable development of resistance and studies that are examining pazopanib in novel settings such as in combination with other drugs and in planned sequences are important and likely to help shape the future for this drug and patient management in general.

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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