Pazopanib in the treatment of renal cell carcinoma

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A variety of novel molecularly targeted drugs have been introduced for the treatment of metastatic renal cell carcinoma (RCC) over the last several years. Pazopanib is the most recent addition and functions as a potent inhibitor of the vascular endothelial growth factor receptor tyrosine kinase. Pazopanib has been studied in two large randomized clinical trials demonstrating the efficacy and tolerability of this drug in RCC. Based on these results, pazopanib has become the sixth targeted agent approved for the treatment of RCC. This review will focus on pazopanib's *in vitro* activity, clinical effectiveness, side-effect profile and how it can be integrated among the other available drugs in the management of RCC.

Keywords: angiogenesis • HIF • mTOR • tyrosine kinase • tyrosine kinase inhibitor • von Hippel–Lindau disease

Tumor angiogenesis is a critical driving factor in the development of metastatic clear cell renal cell carcinoma (RCC) [1]. Increasing knowledge of RCC molecular biology over the last two decades has given insight into the molecular pathogenesis that drives tumor angiogenesis in this deadly cancer [2]. In the 1990s, the tumor-suppressor gene, von Hippel–Lindau (VHL), was found to be frequently mutated or silenced in sporadic RCC cases [3-5]. The protein product of VHL functions in part to regulate two transcription factors, the hypoxia inducible factors (HIF)-1 α and -2 α [6]. In the absence of the functional VHL protein, these transcription factors are allowed to accumulate and ultimately cause the production of a variety of factors that promote tumor cell survival, proliferation and invasiveness [7]. Among the gene targets that are induced with HIF transactivation are VEGF, PDGF, angiopoetin (Ang)-2 and a host of other protein products [8-10]. VEGF, PDGF and Ang-2 are all molecules that take part in proangiogenic signaling pathways as the RCC tumor cell interacts with its stromal environment, with the net effect of VHL loss in RCC causing a highly vascular tumor phenotype. Over the last 5 years, several molecularly targeted drugs that specifically inhibit the VEGF angiogenesis pathway have been introduced for the treatment of RCC [11]. In addition, drugs that target the mammalian target of rapamycin (mTOR) protein have been approved for use in RCC. mTOR is a protein that is downstream of multiple signaling pathways and is upstream of HIF synthesis and the mechanism of action of mTOR inhibitors in RCC is felt, in part, to stem from blockage of HIF production and interruption of growth factor pathway signaling (e.g., VEGF receptor [VEGFR]-2) [12-14].

Currently there are six US FDA approved molecularly targeted agents for RCC, including four that impact the VEGF pathway (sorafenib, sunitinib, bevacizumab and pazopanib), and two that inhibit mTOR (temsirolimus and everolimus) (Figure 1). These drugs have gained approval by improving clinical outcomes (progression-free survival [PFS] or overall survival [OS]) in large Phase III trials that compared the targeted agent to either placebo or interferon [15–20]. Although the clinician has the option of selecting among these agents for the management of their treatment-naive RCC patient, based on the Phase III data available on these agents, one can utilize these

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Figure 1. Key molecular pathways in renal cell carcinoma biology and approved agents that target these pathways. Dark grey boxes represent key molecular events that support renal cell carcinoma tumorigenesis. Light grey boxes show classes of agents that inhibit these pathways. VHL: von Hippel–Lindau; HIF: Hypoxia-inducible factor, mTOR: Mammalian target of rapamycin.

drugs in an evidence-based manner. This review will focus on the clinical development of pazopanib, including its mechanism of action and pivotal clinical studies, and how pazopanib can be distinguished from other available agents and properly placed in the evidence-based management of RCC.

Preclinical evaluation of pazopanib

Pazopanib (VotrientTM, GlaxoSmithKline) is an orally bioavailable potent inhibitor of the tyrosine kinases, VEGFR-1, -2 and -3, PDGF receptor (PDGFR)-α and - β , and c-kit [21]. The inhibitory concentrations (IC₅₀) for kinase inhibition are 10, 30, 47, 71 nM for the kinases VEGFR-1, -2, -3 and PDGFR-β, respectively. This inhibitory profile is similar in terms of VEGFR potency to that of sunitinib, but not quite as potent as seen with the upcoming investigational agents, axitinib and tivozanib (Table 1) [22-26]. In addition, although pazopanib targets several tyrosine kinases, the spectrum of kinase inhibition is not quite as broad as sunitinib or sorafenib, which may explain the difference in toxicity profiles of these agents. Pazopanib has demonstrated anti-angiogenic properties via inhibition of the VEGF pathway in several preclinical models and preclinical findings of anti-tumor effect led to early testing of the drug in patients [21].

Phase I analysis of pazopanib in patients

Initial evaluation of pazopanib in patients involved a Phase I clinical trial in which advanced stage solid tumor patients who had failed available standard therapies were enrolled to receive the drug with end points including dose-finding and safety analysis [27]. In this study 63 patients were enrolled from multiple centers in a nonrandomized, open-label fashion. A total of 43 patients were enrolled to a doseescalation portion of the trial while an additional 20 were involved in a dose-expansion cohort. Eligibility criteria included histologically confirmed advanced solid tumors, life expectancy of more than 12 weeks and adequate performance status and laboratory parameters. Several dosing arms were studied, including dosing of 50-100 mg three-times weekly, 50-2000 mg once daily dosing, and 300-400 mg twice-daily dosing. No maximally tolerated dose was found; however, a plateau in exposure was seen at doses of at least 800 mg daily. Therefore, the dose chosen for future studies was 800 mg by mouth, once daily. During the study, the mean

half-life of pazopanib was found to be around 31 h. Adverse events that were seen with administration of pazopanib included diarrhea, hypertension, nausea and hair depigmentation. In terms of clinical benefit, 17 patients (27%) obtained partial response or stable disease with pazopanib treatment (all responses were seen with doses $\geq 600 \text{ mg/day}$). A total of 12 patients with RCC were included in this Phase I trial. Two of these RCC patients had confirmed partial response, while another four had stable disease. Pharmacodynamic end points of the study included dynamic contrast-enhanced MRI in 12 of the patients in which seven of these had decreased (≥50%) tumor blood flow at 8 days of pazopanib therapy and 10 patients had decreased blood flow at day 22. Based on these findings, a Phase II trial in advanced RCC patients was developed.

Phase II trial in advanced RCC patients

A large open-label, multicenter, randomized Phase II discontinuation study of pazopanib was conducted in advanced RCC patients in order to further define its efficacy and side-effect profile in this disease [28]. This trial included patients with metastatic or locally recurrent clear cell RCC who were treatment naive or had failed a prior cytokine therapy or a single bevacizumab-containing regimen. In order to be deemed eligible, patients had to have predominantly clear cell RCC on histologic examination and have measurable disease as defined by the Response Evaluation Criteria In Solid Tumors (RECIST) criteria. Pazopanib was administered at the predetermined dose of 800 mg

Table 1. Inhibitory profile of pazopanib; other VEGF tyrosine kinase inhibitors are shown below for comparison.									
Agent	Enzyme, IC _{so} (nM)								Ref.
	VEGFR-1	VEGFR-2	VEGFR-3	PDGFR- α	PDGFR-β	c-kit	$Flt-3^{\dagger}$	Raf	
Pazopanib	10	30	47	71	84	74	>2000		[21]
Sunitinib	21	34	3	143	75	40	4		[26]
Sorafenib		90	20		57	68	58	6	[22]
Axitininb [‡]	0.1	0.2	0.1-0.3	5	1.6	1.7	>1000		[25]
Tivozanib [‡]	0.21	0.16	0.24		1.72	1.63			[24]
[†] Inhibition of the Elt-3	kinase is dran	natically differe	nt for nazonar	h compared v	vith sunitinih an	d sorafenih :	and may expl	ain some of the	

differences in toxicity profile among these agents.

*Axitinib and tivozanib have not yet been approved, but have a significantly greater VEGFR inhibitory potency than available agents.

 IC_{50} : Inhibitory concentration; PDGFR: PDGF receptor; VEGFR: VEGF receptor.

daily and it was planned that patients should continue pazopanib treatment or be randomized to either pazopanib or placebo in a predetermined manner. Patients who had response at the first re-evaluation were continued on pazopanib until progression, while those who had stable disease at first re-evaluation were randomized to either continue pazopanib or receive placebo. Planned interim analysis was performed after the first 60 patients had reached the 12-week point in the study. This interim analysis revealed a meaningful response rate for pazopanib of 38% and therefore no further randomized discontinuation was performed and all patients received pazopanib. Only 55 of the total 225 patients enrolled on the entire study underwent randomization.

The primary end point of the trial was evaluation of overall response rate (ORR), with secondary end points including PFS and duration of response. Patients were evaluated for response at week 12 and then every 8 weeks thereafter. The ORR for pazopanib on this trial was found to be 35%. The response rate was similar regardless of whether patients were treatment naive or had received prior cytokine therapy. The secondary end point of duration of response was found to be 68 weeks. The median PFS was 52 weeks (95% CI: 44-60 weeks). Pazopanib therapy was felt to be tolerable with common adverse effects including hypertension, fatigue, nausea and hair depigmentation. Common adverse laboratory events included elevation of liver transaminases. Adverse events were generally low grade; however, grade 3 or 4 adverse events that were seen included hypertension, transaminase elevation, diarrhea and fatigue. Only 31% of patients required dose reduction with approximately 50% of patients who had dose reduction being able to escalate back to full-strength dosing. Given the promising results of this trial, which reaffirmed the drug's effectiveness and tolerability, a large randomized Phase III trial was undertaken.

Phase III study of pazopanib in advanced RCC patients

Based on the activity seen in patients with RCC in the previous Phase II trial, a large, international multicenter Phase III trial comparing pazopanib with placebo for the treatment of patients with metastatic RCC was performed [29]. The patient population accrued for this trial was quite similar to that in the Phase II study. Patients that had confirmed RCC with predominate clear cell histologic features and that were either treatment naive or had received a single prior cytokine therapy were allowed to enter the study. Upon enrollment, subjects were stratified based on performance status (Eastern Cooperative Oncology Group [ECOG] 1 or 0), presence or absence of prior nephrectomy, and previous treatment status (naive or cytokine). A 2:1 randomization was made to either pazopanib 800 mg/day or matching placebo, respectively. PFS was the primary end point of the study. Secondary end points consisted of ORR, OS, duration of response and safety.

In this large Phase III trial, a total of 435 patients were randomized in a 2:1 fashion to receive either pazopanib or placebo. Demographic analysis revealed that in the pazopanib treatment arm, most patients had undergone prior nephrectomy (89%), were treatment naive (53%) and had an intermediate Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification (55%). The unstratified median PFS for the study was 9.2 months for the pazopanib arm compared with 4.2 months for the placebo arm (HR: 0.46; p < 0.0001). Analysis of the PFS with stratification based on prior treatment revealed that median PFS for those patients who were treatment naive was 11.1 months for the pazopanib group and 2.8 months for those on placebo (HR: 0.40; p < 0.0001). Pazopanib resulted in an ORR of 30% (95% CI: 25.1-35.6%) based on independent central review. The presence of prior treatment did not have as major of an impact on response rates, with treatment-naive patients having a response rate of 32% compared with 29% in those treated with prior cytokine therapy. Median duration of response was 58.7 weeks for the pazopanib arm. OS was immature at the time of publication.

Common adverse events included hypertension, diarrhea, hair depigmentation, nausea and vomiting. These effects were similar to that seen in the Phase I and II studies of pazopanib and are anticipated class effects of VEGF receptor tyrosine kinase inhibitors. Laboratory abnormalities were notable for alanine aminotranferease/aspartate aminotransferase (ALT/AST) elevation, hyperglycemia, hypophosphatemia and cytopenias. Adverse events from this trial are reviewed in Table 2. Grade 3 or 4 adverse events were uncommon; however,

Table 2. Adverse events of pazopanib as noted in the Phase III renal cell carcinoma trial.

Toxicity (n = 290)	Any grade		Grade 3/4		
	n	%	n	%	
Clinical-based adverse events					
Diarrhea	150	52	11	4	
Hypertension	115	40	13	4	
Hair depigmentation	109	38	1	0	
Nausea	74	26	2	1	
Anorexia	65	22	6	2	
Vomiting	61	21	7	2	
Fatigue	55	19	7	2	
Asthenia	41	14	8	3	
Abdominal pain	32	11	6	2	
Headache	30	10	0	0	
Laboratory-based adverse events					
ALT elevation	152	53	35	12	
AST elevation	152	53	23	8	
Hyperglycemia	115	41	2	1	
Leukopenia	103	37	0	0	
Hyperbilirubinemia	102	36	9	3	
Hypophosphatemia	95	34	11	4	
Neutropenia	94	34	4	1	
Hypocalcemia	91	33	8	3	
Thrombocytopenia	89	32	3	1	
Hyponatremia	86	31	15	5	
Lymphocytopenia	86	31	12	4	
Hypoglycemia	47	17	1	0	
Hypomagnesemia	31	11	9	3	
Adverse events are listed in order of frequence ALT: Alanine aminotranferease; AST: Aspartate	y of occurrence. Data aminotransferase.	from [29].			

grade 3/4 ALT elevation was seen in 12% of patients. Hepatoxicity in the form of ALT/AST was seen in 53% (all grades) and hyperbilirubinemia was seen in 36% (all grades). It should be noted that most of these patients were asymptomatic and no dose reduction was required. Because of this toxicity signal, a black box warning has been added to the prescribing information for pazopanib warning against potential hepatic toxicity [16]. The majority of transaminase elevations occurred in the first 18 weeks. Given the increased frequency of hepatoxicity with this agent, liver function tests should be performed prior to initiation of therapy and once every 4 weeks for the first 4 months with periodic monitoring thereafter. Thromboembolic events were seen infrequently, with arterial thrombotic events seen in 3% of the patients treated with pazopanib. Quality-of-life surveys were also

performed in the trial and the results of this analysis highlighted the tolerability profile of pazopanib in that no difference was seen in patient's quality of life in the pazopanib arm compared with placebo.

Integration of pazopanib among other agents for the treatment of RCC

The results of the Phase III trial reaffirmed the efficacy and tolerability that pazopanib had displayed in the earlier studies and in October 2009, pazopanib was approved by the US FDA for the treatment of advanced RCC [101]. Being the sixth targeted drug approved for RCC and the fourth drug in the class of VEGF-targeted therapies, finding a place for this drug may be difficult for some clinicians. The patient population in which pazopanib was studied included some patients who were treatment naive and some who had received prior cytokine therapy. In order to appropriately integrate pazopanib among other available agents, it is helpful to understand the settings in which each of these agents have been explored. Agents that were tested in the first-line or treatment-naive setting include sunitinib, temsirolimus, bevacizumab plus interferon and pazopanib. In the secondline or greater setting, sorafenib, everolimus and pazopanib have shown clinical benefit in large studies. The decision of agent sequencing for patients is at the discretion of the practitioner; however, it is helpful to take into context the clinical

data available and the potential side-effect profile of each agent when navigating the options. Table 3 shows the current level 1 evidence for approved targeted agents for RCC and comparison of Phase III study outcomes.

Evidence-based front-line therapies

Sunitinib, a multi-targeted receptor tyrosine kinase inhibitor of VEGFR1–3, PDGFR-α and -β, FLT-3 and c-kit, was approved for advanced RCC in 2006 after analysis in multiple clinical trials [30-33]. Sunitinib showed its effectiveness in a large Phase III randomized trial compared with interferon in treatment-naive patients [16,34]. This trial randomized 750 patients with metastatic clear cell RCC, with a primary end point of PFS. Sunitinib showed a significantly different median PFS of 11 months for those in the sunitinib arm compared with 5 months for those in the placebo arm (HR: 0.42; p < 0.001). Sunitinib had a response rate of 39% by blinded central review and 47% by investigator assessment [34]. The median overall survival for patients receiving sunitinib in this study was 26.4 months compared with 21.8 months for the interferon group (unstratified log rank HR 0.821, 95% CI 0.673-1.001, p = 0.051; stratified log rank HR 0.818, 95% CI 0.669-0.999, p = 0.049). The lack of a statistically significant survival advantage for sunitinib, is probably due to cross-over from the interferon arm to more effective therapies. Side-effects from sunitinib were found to commonly include fatigue, hypertension, nausea,

diarrhea, and hand-foot syndrome. Fatigue, cytopenias and hypertension were among the most common grade 3 or 4 toxicities. The efficacy findings of sunitinib are in the same ball-park as pazopanib which is likely due to the similar targets and potency of the agents. Pazopanib does seem to have a lower frequency of hand–foot syndrome and cytopenia compared with sunitinib which may be explained by its inhibitory profile. In particular, unlike sunitinib, pazopanib does not potently inhibit FLT-3 which is expressed on hematopoietic cells.

Temsirolimus, the first mTOR inhibitor to be approved for RCC, was studied in a Phase III trial in which metastatic RCC patients with poor risk MSKCC features were enrolled [17]. This subset was selected for analysis in the Phase III trial based on evidence of signal in this group in a previous Phase II study [35]. Additionally in the Phase III study, no restriction on histologic subtype was placed on RCC patients who enrolled. Patients were required to be treatment naive and were randomized to receive either single-agent temsirolimus, interferon or a combination of temsirolimus and interferon. OS was the primary end point of the trial and an OS benefit of 10.9 months was seen in the singleagent temsirolimus group compared with 7.3 months in the interferon group (HR: 0.73; p = 0.008). OS for the combination arm was 8.4 months and not statistically different compared with the interferon arm (p = 0.70). PFS was longest in the temsirolimus group compared

Table 3. Organization of approved targeted agents for renal cell carcinoma based on Phase III data.							
Setting	Options based on Phase III data	Primary outcome of Phase III trial	Ref.				
No prior treatment, good or intermediate risk features ⁺	Pazopanib	Improved PFS over placebo, 11.1 vs 2.8 months $^{\scriptscriptstyle \dagger}$	[29]				
	Sunitinib	Improved PFS compared with interferon: 11 vs 5 months, improved OS compared with interferon: 26.4 vs 21.8 months (unstratified log rank test HR 0.821; $p = 0.051$; stratified log rank test HR: 0.818; $p = 0.049$)	[16]				
	Bevacizumab plus interferon	Improved PFS compared with interferon, AVOREN trial: 10.2 vs 5.4 months; CALGB trial: 8.5 vs 5.2 months OS compared with interferon alone: 23.3 vs 21.3 months (unstratified HR: 0.91; $p = 0.3360$; stratified HR: 0.86; $p = 0.1291$)	[19,20]				
No prior treatment, poor risk features ⁺	Temsirolimus	Improved OS compared with interferon, 10.9 vs 7.3 months	[17]				
Prior front-line cytokine	Pazopanib	Improved PFS over placebo, 7.4 vs 4.2 months ⁺	[29]				
	Sorafenib	Improved PFS over placebo, 5.5 vs 2.8 months	[15]				
Prior VEGF inhibitor	Everolimus	Improved PFS over placebo, 4.9 vs 1.9 months	[46]				
Prior mTOR inhibitor	Unknown	Not applicable					
⁺ Based on Memorial Sloan-Kettering	Cancer Center risk criteria definition of	clear cell renal cell carcinoma risk [53].					

"Values are based on stratified analysis, unstratified analysis showed an overall PFS of 9.2 months for the pazopanib group and 4.2 months for place mTOR: Mammalian target of rapamycin; OS: Overall survival; PFS: Progression-free survival. with the interferon and combination groups (5.5, 3.1 and 4.7 months, respectively, independent review). Common side effects from temsirolimus included asthenia, anemia, rash, dyspnea, hyperlipidemia and hyperglycemia. Based on these results, temsirolimus was approved by the FDA in May of 2007 [102]. It is considered a treatment option for patients who meet the criteria for poor risk RCC. Although the trial included patients with histologies other than clear cell, these included only 20% of the trial population and it is unclear what histologies these non-clear-cell RCC patients had and how they fared compared with the patients with clear-cell RCC.

Bevacizumab is a humanized monoclonal antibody that targets the VEGF pathway through binding and clearance of the VEGF ligand. The combination of bevacizumab and interferon has also been approved for the treatment of RCC [103] and this combination has been studied most extensively in the treatment-naive population. Two Phase III studies have been performed evaluating the effectiveness of bevacizumab and interferon compared with interferon alone. In the AVOREN study, a Phase III trial that evaluated the combination of bevacizumab and interferon compared with interferon in 649 patients with predominantly clear cell RCC, an improved PFS was seen in the bevacizumab arm (10.2 vs 5.4 months; HR: 0.63; p = 0.0001) [19,36]. In a similarly designed The Cancer and Leukemia Group (CALGB) Phase III trial, 732 patients with untreated clear cell RCC were randomized to receive bevacizumab and interferon or interferon alone [20,37]. This trial also showed an advantage in PFS for the bevacizumab plus interferon arm with a median PFS of 8.5 months compared with 5.2 months in the interferon arm (HR: 0.71; p < 0.0001). Neither Phase III trial demonstrated a statistically significant OS benefit and this is felt to be secondary to exposure to effective available therapies on the interferon arm after progression. The side-effect profile of the bevacizumab and interferon combination was similar in both studies and commonly included hypertension, fatigue, anorexia and proteinuria. The combination of bevacizumab and interferon was approved by the FDA in July 2009.

• Evidence-based second-line or greater therapies Sorafenib is a multi-targeted tyrosine kinase inhibitor that potently inhibits VEGFR-2 and -3, PDGFR- β , RAF, FLT-3 and c-kit [38-42]. Sorafenib was the first targeted agent to gain approval for the treatment of advanced RCC. In a large Phase III randomized placebo-controlled trial in patients with metastatic RCC that had previously been treated with prior cytokine therapy, 903 patients were randomized to receive sorafenib or placebo [15,43]. The primary end point of this trial was OS with a secondary end point of PFS survival. The overall investigator-assessed response rate for sorafenib was 10% with a clinical benefit rate of 84%. PFS was found to be 5.5 months compared with 2.8 months in the placebo arm (HR: 0.44; p < 0.01). The final OS results did not show improvement in OS for patients treated with sorafenib compared with placebo. Based on the Phase III study, sorafenib has level 1 evidence for use after cytokine failure; however, because of sorafenib and sunitinib's earlier approval than the other agents, these two targeted agents have been commonly used in first- and second-line therapy in the practical management of patients with metastatic RCC. This has resulted in numerous retrospective reports of sorafenib and sunitinib sequential use that supports the lack of cross-resistance between the agents. Common side-effects of sorafenib include hypertension, diarrhea, rash, nausea and hand-foot syndrome.

Everolimus is an orally bioavailable inhibitor of the mTOR complex that has been evaluated in RCC [44,45]. In a Phase III placebo-controlled trial [18,46], 410 patients with metastatic RCC who had previously progressed on sunitinib, sorafenib or both, were randomized in a 2:1 fashion to receive everolimus or placebo. It should be noted that prior treatment with bevacizumab or cytokine therapies was also allowed. The primary end point of this study was PFS. Updated results of this trial showed a statistically significant improvement with everolimus therapy versus placebo (4.9 vs 1.9 months). OS analysis did not demonstrate an improved outcome with the everolimus arm; however, as with the other trials a large portion (81%) crossed over to receive the active agent. Side-effects of everolimus are similar to that expected within the mTOR inhibitor class, with common toxicities including fatigue, anemia, rash, stomatitis, hyperlipidemia and hyperglycemia. Additionally, grade 3 noninfectious pneumonitis was reported in 3% of patients (n = 8). This particular side-effect is a class effect toxicity and has been reported with other mTOR inhibitors. Although the exact mechanism of action for this toxicity is unknown, several hypotheses have been proposed [47].

Placement of pazopanib

Pazopanib has level 1 evidence for use in the first-line treatment-naive management of RCC and in the second-line post-cytokine therapy RCC population. Use of single-agent cytokine therapies are not commonly used in locations where the more active targeted agents are available. Therefore the 'real-life' evidence-based indication for pazopanib is in the front-line setting for low- to intermediate-risk RCC. Of pazopanib, sunitinib or bevacizumab, the agent that is the best option for low- to intermediate-risk RCC patients is still a matter that remains to be reconciled.

Currently, a Phase III noninferiority trial evaluating front-line pazopanib versus sunitinib is ongoing. This trial will better inform us on these two agents. Based on cross-study analysis of pazopanib and sunitinib, they appear quite similar in terms of response rates and PFS end points. Therefore, secondary end points in the ongoing trial such as tolerability may determine the better agent. Additionally, there are trials evaluating the role of continued VEGF inhibition after primary VEGF inhibitor progression versus mTOR inhibitors. Although everolimus is currently the only agent with level 1 evidence for use following VEGF inhibitor failure, the question of continued use of VEGF inhibitors until true VEGF inhibitor refractoriness is observed versus proceeding directly to mTOR inhibition after first-line VEGF inhibitor failure is also unanswered.

Despite these issues, patients should ideally be exposed to all available agents and practical use of these agents involves selection based on drug efficacy, toxicity profile and patient-drug compatibility, taking into account coexisting comorbidities and functional status. Furthermore, translational research continues to advance the field, particularly with the search of molecular-based subsets within clear cell RCC. Use of these molecular markers may further be able to predict which targeted agent, combination of agents or sequence of agents will yield optimal results for any particular RCC patient, resulting in an 'individualized medicine' approach rather than the current broad-based approach. For example a recent study was reported at the 2010 American Society of Clinical Oncology meeting evaluating the use of plasma cytokine and angiogenic factors as potential predictors of response to pazopanib. This study was part of a subset of patients (n = 215) from a Phase II study by Hutson et al.. It involved AVANTRAT biochips to identify candidate plasma cytokine and angiogenic factor biomarkers. The study found that lower baseline levels of HGF and IL-6 were correlated with greater tumor shrinkage and that low HGF, low IL-6 and high E-selectin levels were correlated with longer PFS in RCC patients treated with pazopanib. Although this study requires prospective validation, it is an example of how molecular biomarkers may be used to identify potential responders to targeted therapeutics.

Adjuvant pazopanib for resected RCC

The use of molecularly targeted agents to reduce the risk of recurrence following resection of high-grade or locally advanced RCC is a very appealing prospect, in particular due to the fact that the disease is uniformly fatal if it recurs in the metastatic stage. Previous studies evaluating the use of adjuvant interferon have been unsuccessful. Although it remains unclear whether using these new targeted agents, which commonly result in stable disease and rarely complete responses, will be able to impact longterm outcomes such as survival, several large Phase III studies of adjuvant therapy are ongoing.

In the placebo-controlled S-TRAC study, 1 year of sunitinib therapy is being administered following nephrectomy for clear cell or non-clear-cell RCC (NCT00375674). In another trial, the ASSURE trial, both sorafenib and sunitinib are being explored as single-agent adjuvant therapies compared with placebo in a similar population (NCT00326898). In the SORCE trial, which is being performed in the UK, duration of adjuvant targeted therapy is being evaluated with a design of sorafenib for 1 year versus sorafenib for 3 years versus matching placebos (NCT00492258). All three of these studies are looking at disease-free survival as the primary end point, with OS and quality of life as secondary measures. A similar Phase III adjuvant RCC study is planned for pazopanib. Pazopanib appears to have similar efficacy as sunitinib and therefore the results of the ASSURE and S-TRAC trials may be predictive of the results of this trial, which is planned to start accrual in 2010.

Future perspective

Although molecularly targeted therapies have resulted in a dramatic improvement in response rates, PFS and OS end points compared with cytokine-based therapies and best supportive care, metastatic RCC still remains an incurable disease and complete responses are very rare. In addition, patients invariably develop resistance to targeted agents requiring selection of alternative treatments [48]. As a result, it is critical to optimize the use of currently available therapies to overcome potential resistance pathways and develop new agents that may either have superior single-agent activity to those currently available or that may be combined with available agents to improve clinical outcomes. Several novel agents are currently in late-phase testing, and include the VEGFR tyrosine kinase inhibitors, axitinib and tivozanib, which demonstrate a more potent and selective inhibitory profile. In the next 5 years, it is expected that one of these two agents may become the standard front-line VEGF inhibitor for unselected clear cell RCC patients, based on ongoing Phase III trials. In addition, inhibitors that target potential key VEGF inhibition resistance mechanisms are in development, including the angiopoietin inhibitor AMG386 and the VEGF/FGF inhibitor dovitinib. These agents have the potential to be useful for patients whose tumors become resistant to VEGF therapy depending on the patient's particular VEGF resistance pathway. Furthermore, the incorporation of molecular biomarkers will be crucial in the next several years in order to improve outcomes with currently approved agents by guiding drug selection, as well as to aid in the discovery of unique molecules for future drug development. Two recently reported studies have highlighted the potential for use of genomic-based methods of identifying molecular subsets that can be exploited in this manner [49,50].

The next 5-10 years will also bring much needed answers to the questions of sequencing versus combination approaches to the treatment of metastatic RCC. Several trials are ongoing that will shed light on optimal sequencing. These include the RECORD-3 trial, which will evaluate the sequence of sunitinib followed by everolimus versus everolimus followed by sunitinib (NCT00903175). In addition, the AXIS trial will explore the use of sorafenib versus axitinib in patients who have failed front-line sunitinib (NCT00678392). The Torisel 404 trial similarly will look at sequencing after sunitinib failure, comparing continued VEGF inhibition with sorafenib with the mTOR inhibitor temsirolimus (NCT0047486). Additionally, pazopanib is being evaluated in a Phase II, second-line study following front-line failure of sunitinib or bevacizumab (NCT00731211). The primary end point of this study is overall response rate with a secondary end point of PFS. The outcomes of these sequencing studies will illuminate the optimal sequencing for nonselected RCC patients; however, the more interesting question may pertain to the optimal sequencing for molecular subsets of RCC patients, which could potentially raise the bar even higher.

The role of combination therapy with molecularly targeted agents is also of particular interest in the field. Combinations of VEGF inhibitor plus VEGF inhibitor as well as VEGF inhibitor plus mTOR inhibitor have been performed in a variety of early-phase clinical studies. Combinations of vertical pathway inhibition using two VEGF inhibitors has produced higher response rates in some studies, but has been at the cost of increased toxicity and intolerance. The combination of sunitinib and bevacizumab resulted in higher frequencies of hypertension, proteinuria, thrombocytopenia and other toxicities such as microangiopathic hemolytic anemia and reversible posterior leukoencephalopathy [51]. Recently, the TORAVA study has been reported, which is a Phase II analysis of bevacizumab/temsirolimus versus bevacizumab/interferon versus sunitinib [52]. The primary end point of this study was nonprogression rate at 48 weeks, which was found to be 30.7, 40.5 and 65.9% for each of these arms, respectively. Although the numbers of patients involved in this trial were small, which makes it difficult to interpret the efficacy end points, one notable finding was that of adverse effects. The bevacizumab/temsirolimus combination arm had considerably more grade 3 and 4 toxicities compared with the other two standard arms. One potential criticism of the trial would be that dose reduction of temsirolimus was allowed, while dose reduction of

bevacizumab was not. In the next few years, other combination trials will further expand on the understanding of the effectiveness and feasibility of combination therapies and these include the RECORD-2 trial (bevacizumab/ interferon vs bevacizumab/everolimus; NCT00719264), the INTORACT trial (bevacizumab/interferon vs bevacizumab/temsirolimus; NCT00631371), and the BeST study (bevacizumab vs bevacizumab/temsirolimus vs bevacizumab/sorafenib vs sorafenib/temsirolimus; NCT00378703).

The placement of pazopanib in combination and sequencing trials is also appealing. One potential advantage that pazopanib may have in the development of combination therapies is that it appears to be more tolerable than other available VEGF tyrosine kinase inhibitors. Currently pazopanib is being evaluated in a Phase II study in combination with bevacizumab, which will demonstrate the tolerability and efficacy of these two combined agents (NCT00992121). In addition, it is being studied in other cancer subtypes in a variety of combination regimens including lapatinib, temsirolimus and cytotoxic chemotherapies [104].

In conclusion, pazopanib, an orally bioavailable, inhibitor of VEGFR 1–3, PDGFR- α and - β , and c-kit has been approved for the treatment of metastatic RCC. This agent has been studied in two large randomized trials and proven to be an effective and tolerable therapy for this disease. The recent addition of pazopanib to the armamentarium of agents available for the management of RCC has given the practitioner more options when selecting therapies. Pazopanib is a potent inhibitor of the VEGFR tyrosine kinases, with an inhibitory profile and clinical effectiveness that is similar to sunitinib. One potential advantage that pazopanib may have over sunitinib is better tolerability, although an ongoing clinical trial comparing these two agents headto-head will answer this question. Currently, pazopanib should be considered a standard front-line option for the management of low- to intermediate-risk clear cell RCC. The role of pazopanib in the adjuvant setting also is being studied.

Exploration of unique sequences or combinations of available agents is also being carried out, which will hopefully improve clinical outcomes and teach us about mechanisms of resistance and ways in which these pathways can be overcome through the novel application of agents. Finally, the identification and validation of molecular markers may help to further define subsets of RCC patients that may best respond to agents such as pazopanib and may also be a spring board for other targets to be identified and new agents developed. Metastatic RCC treated with the currently available targeted agents remains an incurable disease and clinical trial participation remains critical to solve these riddles.

Executive summary

- Pazopanib is an orally bioavailable, potent inhibitor of the VEGF receptors 1–3, PDGF and c-kit.
- Pazopanib has shown substantial clinical activity in the treatment of metastatic renal cell carcinoma (RCC), with improvements in response rate and progression-free survival compared with placebo.
- Pazopanib has a similar efficacy rate to sunitinib, with a toxicity profile that may be more tolerable than sunitinib. Currently, a Phase III noninferiority trial comparing these two agents in the front-line management of metastatic RCC is ongoing.
- Pazopanib's toxicity profile is notable for fatigue, hypertension, diarrhea, nausea and liver transaminase elevation. Pazopanib has a black box warning cautioning against liver transaminase elevation.
- Pazopanib is being evaluated in other RCC trials including combination studies and an adjuvant trial.
- Pazopanib should be considered a standard option for RCC patients that are treatment naive or cytokine refractory.
- Future research in RCC includes focus on proper sequencing or combination regimens designed to overcome resistance pathways, as well as molecular biomarker profiling of RCC, which may serve to guide drug selection and predict response.

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