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REVIEW

New agents in renal cell carcinoma

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Abstract Prior to 2005, the treatment options for metastatic renal cell carcinoma (mRCC) were limited. There has been a proliferation of agents since the introduction of sorafenib, sunitinib, and becavicumab for clinical use in advanced renal cell carcinoma. Recently, four new agents have been approved by the US Food and Drug Administration (FDA) for use in mRCC. These agents come from two unique targeted pathways for RCC, tyrosine kinase inhibitors (TKIs) of vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) inhibitors. This review examines the investigational evolution, phases of development, adverse event profiles, and future directions of pazopanib, axitinib, everolimus, and temsirolimus as well as new novel agents being explored in clinical trials for these targeted pathways.

Keywords Renal cell carcinoma · Pazopanib · Axitinib · Everolimus · Temsirolimus · Tyrosine kinase inhibitors · Mammalian target of rapamycin inhibitors

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Introduction

Renal cell carcinoma (RCC) is the seventh most common malignancy among men and the ninth most common among women in the USA. It is estimated that 40,430 new cases of renal cell carcinoma in men and 24,720 in women (total of 65,150) will be diagnosed in the USA. About 50 % of new cases are detected incidentally on radiograph imaging. The 5-year survival for patients who present with metastatic renal cell carcinoma (mRCC) or locally advanced disease is 10–50 %. The mortality estimate for RCC, in 2013, is 13,680/year [1-3].

Previously systemic treatment for advanced RCC has been limited. Hormonal therapy and chemotherapy have been used, but outcomes were unsatisfactory and RCC has shown to be resistant to conventional chemotherapy. Two conventional systemic therapies at this time are immunotherapy and targeted therapy. Historically, the US Food and Drug Administration (FDA)-approved IL-2 and off-label IFN were two cytokines utilized in immunotherapy for RCC. Targeted therapy is now widely used in first- and second-line systemic therapy and is largely replacing cytokine therapy due to improved tolerability and efficacy [4-6].

There are seven targeted agents approved by the FDA to date. Sorafenib was the first targeted agent approved by the FDA in 2005 for RCC, followed by sunitinib, temsirolimus, everolimus, bevacizumab, pazopanib, and most recently axitinib in 2012. These agents can be classified into two categories: vascular endothelial growth factor (VEGF) inhibitors and mammalian target of rapamycin (mTOR) pathway inhibitors.

Sorafenib, sunitinib, bevacizumab, pazopanib, and axitinib are VEGF/VEGFR inhibitors. They are small-molecule tyrosine kinase inhibitors (TKIs) except bevacizumab which is a VEGF ligand inhibitor. Many TKIs and mTOR inhibitors are

still in development in clinical trials for the treatment of advanced RCC.

This review of targeted therapy will focus on four of the newest FDA-approved agents (pazoponib, axitinib, everolimus, and temsirolimus (Table 1). Newer novel agents in development in the TKI class will be discussed as well.

Tyrosine kinase inhibitors

The importance of angiogenic pathways in the biology of RCC is well established [7]. The loss of function of the von Hippel–Lindau (VHL) gene in RCC leads to dysregulation of the VEGF pathway, VEGF protein overexpression, and increased tumor angiogenesis [8]. VEGF is the strongest pro-angiogenic protein, and inhibiting VEGF has been proven to have clinical value in many malignancies, including mRCC [7]. TKI inhibitors are small molecules that inhibit clinical activity in RCC by blocking the intracellular domain of the VEGFR.

Pazopanib: phases of development

Pazopanib is an oral multitargeted TKI, with potent inhibitory activity against VEGFR-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-α, PDGFR-β, and c-kit [9]. It has demonstrated less potent inhibition of several other tyrosine kinases [9]. A phase I multicenter, open-label, nonrandomized, dose-finding trial of GW786034 (pazopanib) was conducted in 63 patients with relapsed or refractory solid tumors [10]. These patients were enrolled into sequential dose-escalating cohorts, ranging from 50 mg three times weekly to 200 mg daily. Twelve patients (19 %) had RCC. Of the 12 patients, 2 achieved partial response (PR) with duration response of 6 and 12.8 months, respectively. There were also four patients who had stable disease. Patients with RCC who experienced partial response or stable disease received doses of ≥800 mg once daily or 300 mg twice daily [10]. The recommended phase II dose was 800 mg once daily.

These results led to a phase II, single-arm, open-label trial. The study enrolled 225 patients with mRCC; 155 patients (69 %) were treatment naïve, and 70 patients (31 %) had

Table 1 Mechanism of action, dosing, and side effects of recently FDA-approved medications for the treatment of metastatic renal cell cancer

Drug	Mechanism of Action	Dosing	Common/Major Side Effects	Indication
Temsirolimus	mTOR inhibitor	25 mg IV weekly	Asthenia/fatigue Anemia Nausea Rash Anorexia Hyperglycemia Dyspnea Infection	Advanced RCC (poor prognosis by MSKCC)
Everolimus	mTOR inhibitor	10 mg PO daily	Stomatitis Infections Pneumonitis Asthenia/fatigue Diarrhea Dyspnea Anemia Hyperglycemia Hypophosphatemia	Advanced RCC after failure with first-line TKI (sunitinib or sorafenib)
Axitinib	Multitargeted tyrosine kinase inhibitor (TKI) against VEGF	10 mg PO BID	Diarrhea Hypertension Hypothyroidism	Advanced RCC (second line)
Pazopanib	Multitargeted tyrosine kinase inhibitor (TKI) against VEGF, PDGFR, c-kit	800 mg PO daily	Diarrhea Hypertension Hair color changes Nausea Anorexia Vomiting	Advanced RCC (first-line)

received one prior cytokine- or bevacizumab-containing regimen [11]. The response rate was 34 % in the treatment-naïve patients and 37 % in patients who had one previous treatment for an overall response rate (ORR) of 35 %. The median progression-free survival (PFS) attributable to pazopanib was estimated to be 52 weeks.

Pazopanib had demonstrated monotherapy activity in patients with RCC in phase I/II trials leading to a randomized, double-blind, placebo-controlled phase III study [12]. Patients were randomized in a 2:1 ratio to receive either 800 mg pazopanib once daily or placebo. The primary end point was PFS. The secondary end points included confirmed ORR, duration of response, and safety [12]. Of the 435 patients with advanced and/or mRCC (233 treatment naïve, 202 cytokine-pretreated), 290 patients were randomly assigned to pazopanib and 145 were randomly assigned to placebo [12]; 227 patients in the pazopanib arm and 131 patients in the placebo arm discontinued treatment at the time of final analysis. At the final PFS analysis, 148 patients progressed on pazopanib and 98 patients progressed on placebo [12]. Pazopanib significantly prolonged PFS compared to placebo (median PFS, 9.2 months vs 4.2 months; $p < .0001$). In the treatment-naïve subpopulation, the median PFS was 11.1 months vs 2.8 months ($p < .0001$), and in the cytokine-pretreated subpopulation, the median PFS was 7.4 months vs 4.2 months ($p < .001$) [6]. The interim overall survival (OS) results did not show either superiority or futility [12]. The response rate for pazopanib-treated patients was 30 %, with 32 % in the treatment-naïve and 29 % in cytokine-pretreated population [12].

The COMPARZ trial is a phase III randomized trial comparing pazopanib to sunitinib in the front-line setting. Patients (1,110) were randomized 1:1, pazopanib 800 mg orally daily continuous dosing vs sunitinib 50 mg orally daily for 4 weeks followed by 2 weeks off treatment (6-week cycles). The primary end point evaluated was noninferiority in PFS between pazopanib and sunitinib. Secondary end points included safety, OS, ORR, duration of response, and time to response. Pazopanib demonstrated noninferiority to sunitinib by independent review (median PFS, 8.4 months vs 9.5 months) and investigator review (median PFS, 10.5 months vs 10.2 months) [13]. The median 2-year OS was 28.4 months for pazopanib vs 29.3 months for sunitinib [13]. ORR was 31 % pazopanib vs 25 % sunitinib [13].

The PISCES study was presented at ASCO 2012 by Dr. Bernard Escudier and colleagues. This randomized trial compared patient preference for pazopanib or sunitinib for first-line treatment of mRCC and should be viewed as an adjunct to the COMPARZ trial [14]. One hundred sixty-nine patients were randomly assigned to receive 800 mg of pazopanib for 10 weeks with a 2-week washout period prior to 50 mg of sunitinib for 10 weeks, or vice versa. Fifty-four patients were assigned pazopanib first, and 60 patients were assigned to sunitinib first. There was a 49.3 % difference in preference between the two drugs with 70 % of patients preferring pazopanib and 22 % of patients preferring sunitinib ($p < 0.001$) [14].

FDA approval

In 2009, the FDA approved the use of pazopanib for the treatment of advanced RCC based on the international, multicenter, randomized, double-blind trial. Pazopanib is a category 1 recommendation in the first-line setting and category 1 in subsequent lines after the use of cytokine therapy per National Comprehensive Cancer Network (NCCN) guidelines [15].

Safety data

The first phase III pazopanib trial demonstrated grade 1/2 adverse event (AE): diarrhea (52 %), hypertension (HTN) (40 %), hair color changes (38 %), nausea (26 %), anorexia (22 %), and vomiting (21 %). The most common grade 3/4 AE were HTN (4 %) and diarrhea (4 %). Arterial thrombotic events occurred in 3 % of pazopanib-treated patients (MI/ischemia (2 %), CVA (<1 %), and TIA (<1 %)) compared with none in the placebo arm. The incidence of hemorrhagic events was 13 % vs 5 % favoring the placebo arm. Fifty-two (18 %) pazopanib-treated patients experienced ALT ≥3× ULN. ALT elevation recovered to ≤grade 1 after dose modification, interruption, or discontinuation in 45 patients (87 %); 7 patients (13 %) did not have adequate follow-up data to assess recovery. Of the patients, 4 % in the pazopanib arm and 3 % in the placebo arm had death-associated with AE. Four patients (1 %) in the pazopanib arm had fatal AE attributable to ischemic stroke, abnormal hepatic function and rectal hemorrhage, peritonitis/bowel perforation, and abnormal hepatic function [12]. These findings led to a black box warning of pazopanib for severe or fatal hepatotoxicity.

Based on the COMPARZ trial, the most common AEs were diarrhea (63 % with pazopanib vs 57 % with sunitinib), HTN (46 % vs 41 %), fatigue (55 % vs 63 %), nausea (45 % vs 46 %), and hand–foot syndrome (29 % vs 50 %) [P5]. The most common lab abnormalities were ALT elevation (60 % vs 43 %), AST elevation (61 % vs 60 %), albumin elevation (33 % vs 42 %), creatinine elevation (32 % vs 46 %), hyperglycemia (54 % vs 57 %), leukopenia (43 % vs 78 %), neutropenia (37 % vs 68 %), thrombocytopenia (41 % vs 78 %), lymphopenia (38 % vs 55 %), and anemia (31 % vs 60 %) [13].

Future direction of pazopanib

The PROTECT trial is an ongoing phase III study to evaluate whether pazopanib compared with placebo can prevent or

delay recurrence of kidney cancer in patients with moderately high or high risk of developing recurrence after undergoing kidney cancer surgery. The primary end point is disease-free survival (DFS). A total of 1,500 patients are estimated to enroll, and the estimated primary completion date is October 2015 [16]. SWITCH-II is a phase III sequential open-label study to evaluate the efficacy and safety of sorafenib followed by pazopanib vs pazopanib followed by sorafenib in the treatment of advanced/metastatic renal cell carcinoma. A total of 544 patients are estimated to enroll, and the estimated primary completion date is June 2016 [16].

Axitinib: phases of development

Axitinib is a potent, selective, second-generation inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3 that blocks VEGFRs at subnanomolar drug concentrations. The relative potency of axitinib is 50 to 450 times greater than that of the first-generation VEGFR inhibitors [8]. Preclinical data suggest that axitinib has antitumor activity that seems to result from its antiangiogenic activity, which is reversible when treatment is discontinued [17]. An initial phase 1 study investigated the safety, clinical activity, and pharmacokinetics (PK) of AG-013736 (axitinib) [18]. Thirty-six patients with advanced solid tumors were enrolled, and six patients (17 %) had RCC. Patients received oral doses ranging from 5 mg twice daily (BID) to 30 mg BID. The primary objective was to determine dose-limiting toxicity (DLT) and the maximum tolerated dose (MTD) of AG-013736 [18]. The primary DLT observed was hypertension occurring in 22 patients (61 %). Eleven patients (30 %) had grade 3–4 HTN. The incidence and severity of HTN was dose dependent. Other DLTs included four patients (12 %) with increased liver function tests (all of which were grade 3–4), fatigue in ten patients (28 %), diarrhea in six patients (17 %) (one grade 3–4), and stomatitis in four patients (11 %) (grade 3–4 in two patients) [18]. Two patients with RCC had confirmed partial responses. Another patient with RCC had decreased tumor burden that did not qualify by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria for a response of 4 months. The recommended phase II dose of the agent was 5 mg orally (PO) twice a day.

Two phase II trials of axitinib in mRCC have suggested potent antitumor activity [19]. The first trial enrolled 52 patients with cytokine-refractory mRCC [19]. The primary end point was ORR. Secondary end points were duration of response, time to progression, OS, and safety. The starting dose was 5 mg PO twice a day. After a median survival follow-up of 31 months, 38 patients had progressed or died. The median time to progression was 15.7 months [17]. Twenty-four patients were still alive at the time of the final analysis, and median overall survival was 29.9 months [17]. The 1-year survival was 78.8 %. The observed ORR was 23 patients (44.2 %), including 2 patients with complete responses. The median response duration was 23 months. Of the 23 patients who initially responded, 12 progressed with response duration ranging from 4.2 to 26.5 months [17].

The second trial was a single-arm, multicenter, open-label trial in which 62 patients with sorafenib-refractory mRCC were assessed. One prior therapy was received by 16 (25.8 %) patients, and 46 (74.2 %) received at least two prior therapies. Majority of patients, 85.5 %, received sorafenib as the only or final treatment [20]. The primary end point was ORR. The secondary end points included safety, duration of response, PFS, and OS. The starting dose was 5 mg PO twice daily, with up to 53.2 % of patients titrating up to 10 mg PO twice a day. Fourteen patients achieved a PR, which provided an ORR of 22.6 % [20]. The median PFS and OS were 7.4 and 13.6 months, respectively. Median follow-up was 22.7 months. The median duration of response was 17.5 months. Eleven patients had stable disease.

The phase III AXIS trial was designed to evaluate axitinib in the second-line therapy setting [8]. In this trial, 723 patients with mRCC who had failed only one previous line of therapy were evaluated. The primary end point was PFS. Secondary end points included OS, ORR, and duration of response. Patients were randomized 1:1 to either sorafenib 400 mg twice daily or axitinib, with starting doses of 5 mg twice daily, increasing to 7 mg twice daily, and ultimately 10 mg twice daily, as tolerated [19]. Results demonstrated a PFS of 6.7 months for axitinib vs 4.7 months for sorafenib ($p < .0001$) [8]. PFS favored axitinib in both the prior cytokine (12.1 months vs 6.5 months, $p < .0001$) and sunitinib (4.8 months vs 3.4 months, $p = .0107$) therapy subgroups [19]. ORR was higher with axitinib compared with sorafenib (19.4 % vs 9.4 %, $p = .0001$) [19]. The median duration of response was 11 months for axitinib and 10.6 months for sorafenib [8]. Overall survival data was presented at the *European Society for Medical Oncology* (ESMO) in 2012 in abstract form and recently published in *Lancet Oncology* failing to demonstrate a survival benefit in favor of axitinib over sorafenib [21]. Median OS was 20.1 months with axitinib vs 19.2 months with sorafenib (hazard ratio (HR) 0.969, $p = 0.37$) [21].

FDA approval

In 2012, the FDA approved the use of axitinib in the second-line setting for advanced RCC based on the randomized, open-label, multicenter phase III AXIS trial.

Safety data

The AXIS trial treatment-related AEs of grade 3 or higher in both arms were fatigue (11 % with axitinib vs 5 % with sorafenib) and gastrointestinal symptoms, including diarrhea (11 % vs 7 %) [19]. The most common AEs noticed in the

axitinib arm were hypertension (grade 3 or higher, 16 % vs 11 %) and hypothyroidism (all grades 19 % vs 8 %) [19].

Future direction of axitinib

Currently, there is an ongoing phase III study comparing axitinib and sorafenib in treatment-naïve patients with mRCC. The primary end point of this study is PFS, and a total of 447 patients are anticipated to accrue by April 2014 [16]. The Adjuvant Axitinib Therapy of Renal Cell Cancer in High Risk Patients (ATLAS) trial is a phase III study. The purpose of this trial is to determine if adjuvant therapy with axitinib will prevent or delay the recurrence of renal cell cancer after surgery to remove the primary tumor in high-risk patients. The primary end point of this study is DFS, and a total of 592 patients are anticipated to accrue by June 2017 [16].

Mammalian target of rapamycin inhibitors

mTOR is a downstream effector of the PI3-K/Akt/mTOR pathway that regulates cell growth and metabolism as a result of environmental factors (i.e., nutrient and energy depletion, oxidative or hypoxic stress, proliferative and survival signaling). Rapamycin (sirolimus), a macrolide antibiotic produced by *Streptomyces hygroscopicus*, was first discovered in 1975 from soil in Rapa-Nui (formerly known as Easter Island) [22, 23]. TOR was later discovered in yeast in 1991 [24]. The mammalian homolog was subsequently identified, cloned, and named mTOR.

Rapamycin binds to an intracellular protein FKBP12, and the resultant protein–drug complex inhibits mTOR kinase activity [25]. The inhibition of the PI3-K/Akt/mTOR pathway results in an immunosuppressive, antifungal, and anticancer activity [25]. The immune-suppressant properties of rapamycin were prioritized, leading to FDA approval in 1999 for prevention of transplant rejection.

Derivatives of rapamycin, called rapalogs, have been synthesized in hopes of utilizing pharmaceutical properties aimed at anticancer tumor cell proliferation and angiogenesis. Two rapalogs, temsirolimus and everolimus, have been developed and evaluated in RCC.

Everolimus: phases of development

Everolimus was approved in 2003 for the prevention of transplant rejection in renal and cardiac patients in Europe. Everolimus is an orally administered inhibitor of mTOR, synthesized as a derivative of rapamycin originally known as SDZ RAD, developed to evaluate its pharmacologic properties [26]. The relative potency of everolimus is at least as active in vivo as rapamycin. Attention turned towards evaluation in solid tumors based upon preclinical studies demonstrating inhibition of proliferation in vitro as well as in in vivo models. A phase I dose escalation study of RAD001 (everolimus) established DLT, tolerability, and optimal dosing via pharmacokinetic and pharmacodynamic studies. Ninety-two patients with advanced solid tumors refractory to standard therapy were enrolled, and ten patients (11 %) had RCC. In part one, patients received oral doses ranging from 5 to 30 mg weekly in four-person cohorts. No DLT was seen during part one. A dose–response relationship between oral administration of everolimus and inhibition of SKG1, an important downstream effector of cell transcription, indicated sustained activity over 7 days at doses ≥20 mg/week [27]. Part two of the study explored 50 to 70 mg/week and 5 to 10 mg/day dosing without identifying MTD. Five of the ten RCC patients demonstrated PFS at 6 months, with one of the aforementioned patients in PR [27]. DLT occurred in one of six patients at 50 mg weekly due to stomatitis and fatigue. DLT occurred in none of four patients at 70 mg; however, grade 4 thrombocytopenia and grade 3 pneumonitis, neutropenia, hyperglycemia, and fatigue were seen. DLT occurred in none of the four patients at 5 mg daily and in one of six patients at 10 mg daily due to hyperglycemia. Nineteen grade 3 or 4 toxicities were reported with stomatitis, thrombocytopenia, and hyperglycemia being the most common. The recommended phase II dose of the agent was 10 mg PO daily [28].

A phase II study evaluated everolimus at a dose of 10 mg daily without interruption in clear cell mRCC with measurable disease receiving ≤1 prior therapy. The primary end point was PFS. Secondary end points were duration of response, safety, toxicity, and OS. Responses were assessed according to RECIST. Fourty-one patients were enrolled; 37 were evaluated for efficacy. Median PFS was 11.2 months and median was OS 22.1 months. Fourteen percent of patients experienced a PR, with a majority (70.3 %) demonstrating PFS ≥6 months. Of the five patients with PR, the median PFS was 17.3 months with a range or response from 8.3 to 37.5 months. For the 21 patients with stable disease for a period ≥6 months, the median PFS was 17.1 months with a range of 6 to ≥36 months. The most common adverse events (>25 %) included nausea, anorexia, diarrhea, stomatitis, pneumonitis, and rash. Grade 3 or 4 adverse events included pneumonitis (18 %), transaminase elevations (10 %), thrombocytopenia and hyperglycemia (8 %), and hyperlipidemia (5 %) [29].

The RECORD-1 trial conducted by Motzer et al. [30] was a phase III randomized, double-blind, placebo-controlled trial of everolimus in patients with mRCC whose disease had progressed on prior VEGF-targeted therapy. Patients were randomized in a 2:1 ratio to receive everolimus 10 mg daily or placebo plus the best supportive care. The trial was halted early during the second interim analysis with a notable median PFS of 4 months vs 1.9 months in favor of everolimus. Only 1 % of patients experienced PR for the best objective response. On final analysis of the Motzer trial, everolimus

provided a 3-month PFS benefit (4.9 months vs 1.9 months). Time to deterioration of 10 % by the Karnofsky performance status (KPS) favored everolimus; median time was nearly 6 months. The everolimus group showed a trend towards improvement in quality of life (HR 0.75, confidence interval (CI) 0.53–1.06). No difference in OS was demonstrated (14.8 months vs 14.4 months); however, 80 % of patients in the placebo arm crossed over to open-label everolimus upon progression [30].

FDA approval

In 2009, the FDA approved everolimus for the treatment of patients with advanced RCC after failure of treatment with first-line VEGFR TKI therapy (sunitinib or sorafenib) based upon the results of RECORD-1.

Safety data

The most common adverse events (≥30 %) from the RECORD-1 trial included stomatitis, infections, asthenia, fatigue, diarrhea, and cough. Grade 3 or 4 toxicity (≥5 %) included infections, fatigue, dyspnea, anemia, lymphopenia, hyperglycemia, and hypophosphatemia. Pneumonitis was a significant adverse clinical event with an average time to development of 4 months. Fourteen percent experienced non-infectious pneumonitis, 4 % of which sustained grade 3 pneumonitis [31].

Dose delay or reduction occurred for clinically significant hematologic or adverse events deemed to be everolimus-related. Per protocol nomogram, a reduction in the dose to 5 mg once daily was permitted. At least one dose reduction occurred in 7 %; at least one treatment interruption occurred in 38 % of everolimus-treated patients. Thirty-six out of the 274 patients (13 %) in the everolimus arm discontinued therapy due to adverse events. Four deaths were disease progression-unrelated. Three of the deaths were infection-related; the fourth patient had grade 3 interstitial lung disease that upon disease progression resulted in acute respiratory failure [31]. Serious adverse events should result in early treatment interruption and can be restarted at a reduced dose of 5 mg/day if there is an improvement to grade 2 or better of the complicating toxicity.

Future direction of everolimus

Everolimus is being evaluated in a number of studies including combination with VEGF-directed therapies, optimization of therapy sequence, and nonclear cell RCC. Other studies involve the use of everolimus in the adjuvant setting to decrease recurrence risk [32]. CALGB 90802 is a randomized phase III trial comparing everolimus plus bevacizumab in the experimental arm vs everolimus plus placebo for patients with advanced RCC progressing after treatment with TKIs. The study is active but no longer recruiting with 700 patients enrolled. The primary end point is OS with expected completion in 2019 for final data collection for primary end point [16]. RECORD-3 is a phase II trial investigating the optimal sequencing of first-line everolimus followed by second-line sunitinib vs the reverse sequencing for mRCC patients who have received no prior systemic therapy. Efficacy and safety data will be reported. This study is ongoing but not recruiting patients. Estimated date of completion was December 2012; however, no data has been reported yet [16]. EVEREST is a phase III trial evaluating everolimus against placebo in the adjuvant setting after surgery. The primary end point is recurrence-free survival; estimated enrollment is 1,218 patients with an expected completion date of 2021 [16].

Temsirolimus: phases of development

Temsirolimus, a rapamycin ester, is an mTOR inhibitor that binds with high affinity to intracellular FK 506-binding protein (FKBP), resulting in a protein–drug complex that inhibits the kinase activity of mTOR [33]. CCI-779 (temsirolimus) mediates its effects through changes in downstream effectors of mTOR, resulting in G_1 phase cell cycle arrest [34]. Preclinical data demonstrated CCI-779 activity against human tumor types in vitro and in vivo nude xenografts [35].

A phase I study evaluated weekly CCI-779 in 16 patients with advanced solid tumors. Dosing ranged from 7.5 to 220 mg/m^2 IV weekly over a 30-min infusion. One patient with mRCC had a PR at 15 mg/m^2; two patients with mRCC had disease stabilization. No DLT was observed. Common side effects included skin toxicity, mucositis, nail changes, hypertriglyceridemia, hyperlipidemia, and thrombocytopenia [36].

A phase II randomized, multiple-dose-level study evaluated CCI-779 in 111 advanced refractory RCC patients by Atkins et al. [37]. More than 90 % had received prior immunotherapy, while 80 % had prior nephrectomy. Randomization to three arms at dose levels of 25, 75, or 250 mg IV weekly were done to evaluate for tumor response, time to progression, survival, and adverse events. ORR was 7 % (one complete response, seven partial responses), median time to progression was 5.8 months, and median survival was 15 months. Common adverse events included rash, mucositis, asthenia, and nausea. Most frequent grade 3 or 4 events included hyperglycemia, hypophosphatemia, anemia, and hypertriglyceridemia. CCI-779 dose level did not affect efficacy or toxicity significantly.

Based upon the 15-month median survival and suggestion of biologic activity of CCI-779, the patients from the Atkins trial were assessed retrospectively, separating patients into good-risk, intermediate-risk, and poor-risk groups as proposed by Motzer et al. [38]. Of the patients, 87 % were classified as intermediate (43 %) or poor risk (44 %). Patients in higher risk

groups had a 1.6- to 1.7-fold longer survival when compared to first-line interferon treatment. This advantage was not seen in the good-risk group; however, only eight patients were represented.

A phase III study of 626 patients with previously untreated mRCC randomized patients into three arms in equal proportions [39]. Patient inclusion required meeting three of six criteria as defined by the modified Memorial Sloan-Kettering Cancer Center Experience MSKCC risk stratification by Motzer et al. (Table 2) [38]. Interferon (18 million U thrice weekly (TIW)), temsirolimus (25 mg IV weekly), or IFN (6 million U TIW) in combination with temsirolimus (15 mg IV weekly) were the treatment allocation arms. The primary end point was OS on an intention-to-treat basis.

Two thirds had prior nephrectomy, 82 % had a KPS≤70, 74 % classified as poor risk (≥3 of 5 factors), and 26 % were intermediate risk (1 or 2 of 5 factors) according to the MSKCC classification. Clear cell carcinoma was the histologic subtype in nearly 80 %, while nonclear cell carcinoma was represented by 20 %.

Median survival was 7.3 months in the interferon group, 10.9 months in the temsirolimus group, and 8.4 months in the combination group. The hazard ratio for death showed significance for the temsirolimus-alone group compared with the interferon-alone group (HR 0.73, CI 0.58–0.92; $p=0.008$). There was no difference for the combination group vs interferon alone. ORR was 4.8 %, 8.6 %, and 8.1 % for interferon, temsirolimus, and combination therapy, respectively. Median PFS by independent radiologic analysis was 3.1, 5.5, and 4.7 months. The temsirolimus-alone group compared to the interferon-alone group had a HR of 0.66, $p=0.001$ in terms of PFS. Approximately 40 % demonstrated PFS≥6 months in the temsirolimus-alone group. In summary, treatment with temsirolimus resulted in longer median OS and PFS compared with interferon, while the combination arm did not yield improvement in OS compared with interferon alone [39]. Subgroup analysis showed a statistical benefit towards temsirolimus for those <65 years of age, with KPS≤70 %, no prior nephrectomy, and nonclear cell histology.

Table 2 Prognostic factors for the stratification of high-risk patients according to modified criteria used as inclusion criteria

* <1-year disease-free interval

* Karnofsky perfromance index between 60 and 70 %

* Hemoglobin below lower level of normal

* Corrected calcium of more than 10 mg/dl

* Lactate dehydrogenase (LDH) level of more than 1.5× the upper limit of normal

* More than one metastatic site of disease

Three or more of six criteria classify patients as high-risk, poor-prognosis RCC. Criteria adapted from Clin Cancer Res 2004; 10: 6302S-6303S.

FDA approval

In May 2007, temsirolimus was approved for the treatment of poor prognosis by the MSKCC risk criteria, treatment-naïve mRCC based upon the phase III trial by Hudes et al. [39]. Per NCCN guidelines, it is a category 1 recommendation for poor-prognosis advanced RCC patients with both clear and nonclear cell histology [15].

Safety data

The most common adverse events (≥30 %) from the Hudes et al. [39] trial were asthenia, rash, anemia, nausea, and anorexia in the temsirolimus arm. Grade 3 or 4 toxicity (≥5 %) included anemia (20 %), asthenia (11 %), hyperglycemia (11 %), dyspnea (9 %), pain (5 %), and infection (5 %). Dose delay occurred in 137 of 209 (66 %) patients on temsirolimus. At least one dose reduction was required in 48 patients (23 %). Per the protocol, temsirolimus was withheld for grade 3 or 4 adverse events according to NCI CTCAE version 3 and restarted at a reduced dose after recovery to grade 2 or lower. For grade 2 events that were poorly tolerated, dose reduction without interruption was permitted by the treating physician. Treatment was discontinued due to an adverse event in 7 %, symptomatic deterioration in 7 %, patient request in 4 %, and a total of six deaths (3 %) while on therapy. The deaths associated with temsirolimus administration included interstitial lung disease (ILD), bowel perforation, and acute renal failure [40]. Serious adverse events should result in early treatment interruption and can be restarted at a reduced dose of 5 mg/week if there is an improvement to grade 2 or better of the complicating toxicity. Doses should not be reduced below 15 mg/week [41].

Future direction of temsirolimus

Temsirolimus is being evaluated in ongoing clinical studies looking at optimal sequencing in patients who have failed initial TKI therapy, combination therapy with TKI and VEGF-targeted agents, biomarker predictors for response and survival with temsirolimus, and nonclear cell histology RCC [32]. Torisel 404 is a phase III trial evaluating sequencing with temsirolimus vs sorafenib in patients who have failed initial therapy with sunitinib. The primary end point is PFS. The study has completed enrollment and the estimated date of completion is 2014 [16]. The BeST trial is a four-arm randomized phase II study of VEGF, RAF kinase, and mTOR combination targeted therapy looking at PFS. Two arms of the BeST trial involve temsirolimus plus bevacizumab and temsirolimus plus sorafenib. The estimated completion date is June 2013 for primary outcome measure [16]. INTORACT is an open-label phase III trial comparing temsiorlimus plus bevacizumab against bevacizumab plus IFN-α for first-line treatment of patients

with advanced RCC. The primary end point of evaluation is PFS. This study has completed enrollment with the estimated completion date in December 2013 [16].

Novel agents in clinical trials

Many oral small-molecule TKIs and PI3-K/mTOR inhibitors are being studied as single agent or in combination trial with FDA-approved targeted agents. Dovitinib and tivozanib are two TKIs in phase III trials and the final results are pending. Other TKIs, cediranib, regorafenib, and linifanib, are in phase I/II trials (Table 3).

Tyrosine kinase inhibitors

Dovitinib (TKI-258) is an oral TKI, which targets VEGFR, fibroblast growth factor receptor (FGFR), and PDGFR. It has both antitumor and antiangiogenic activities. In a phase I trial, patients with mRCC previously treated with at least one VEGF inhibitor, mTOR inhibitor, and immunotherapy received dovatinib and were evaluated for safety and tolerability of the drug. Out of 20 patients, 2 patients had partial response and 12 had stable disease. Reported adverse events from phase I are nausea, diarrhea, vomiting, asthenia, hypertensive crisis, and bradycardia. In a phase I study, 500 mg on a 5-day-on/2 day-off schedule was reported as tolerable [42]. In a phase II study, 51 mRCC patients treated with dovatinib were assessable for tumor response; 4 patients had partial response, 19 patients had stable disease ≥4 months, 11 patients had progressive disease, and results of 7 patients were unknown. Reported PFS was 6.1 months and OS was 10.2 months [43]. It is currently in phase III trial to be compared with sorafenib in terms of safety and efficacy [44].

Tivozanib (AV-951) is another oral TKI also in phase III trials. It targets multiple VEGFR receptors and has been shown

Table 3 Current ongoing clinical trials for metastatic RCC

Drug	Targets	Ongoing renal cancer trials	Phase
Dovitinib (TKI-258)	VEGFR-1, VEGFR-2, VEGFR-3, FGFR, PDGFR-β	Dose escalation study investigating everolimus and dovitinib in metastatic clear cell renal cancer (DEVELOP) (NCT01714765)	1
		Study of dovitinib vs sorafenib in patients with metastatic renal cell carcinoma (NCT01223027)	3
		First-line activity of dovitinib and correlation with genetic changes in RCC (DILIGENCE-1)	2
Tivozanib (AV-951)	VEGFR-1, VEGFR-2, VEGFR-3	A study of tivozanib, and oral VEGF receptor tyrosine kinase inhibitor, in the treatment of renal cell carcinoma (NCT00502307)	2
		A subject treatment preference study of tivozanib hydrochloride vs sunitinib in subjects with metastatic renal carcinoma (TAURUS) (NCT01673386)	2
		A phase 1b, open-label, dose-finding study to evaluate the safety of tivozanib in combination with temsirolimus in subjects with metastatic renal cell carcinoma (NCT00563147)	1
		A biomarker study of tivozanib in subjects with advanced renal cell carcinoma (NCT01297244)	2
		A study to compare tivozanib to sorafenib in subjects with advanced renal cell carcinoma (TIVO-1) (NCT01030783)	3
		An extension treatment protocol for subjects who have participated in a phase 3 study of tivozanib vs sorafenib in renal cell carcinoma (NCT01076010)	3
Cabozantinib (XL 184)	VEGFR-2, MET	Randomized, controlled study of cabozantinib (XL184) vs everolimus in subjects with metastatic renal cell carcinoma that has progressed after prior VEGFR tyrosine kinase inhibitor	3
Cediranib (AZD-2171)	VEGFR-1, VEGFR-2, VEGFR-3	Cediranib in metastatic or recurrent renal cell carcinoma (NCT00423332)	2
		AZD2171 in treating patients with progressive locally recurrent or metastatic kidney cancer that cannot be removed by surgery (NCT00227760)	2
		Gamma-secretase inhibitor RO4929097 and cediranib maleate in treating patients with advanced solid tumors (NCT01131234)	1
Regorafenib (BAY-73-4506)	VEGFR-2, VEGFR-3, Ret, c-kit, PDGFR, and Raf	A phase II uncontrolled study of BAY73-4506 in previously untreated patients with metastatic or unresectable RCC (NCT00664326)	2
Linifanib (ABT-869)	VEGFR, PDGFR	Study of ABT-869 in subjects with advanced renal cell carcinoma who have previously received treatment with sunitinib (NCT00486538)	2

All studies can be found using the listed identifier on the US National Institutes of Health website www.clinicaltrials.gov

to have antitumor activities. In a phase II study with 272 patients with advanced or mRCC, tivozanib was administered for 16 weeks. The reported ORR was 18 % (95 % CI, 14–23 %). In this randomized discontinuation study, 118 patients who had <25 % tumor change after 16 weeks of treatment were randomly further assigned to continue tivozanib or to receive placebo. Out of these 118 patients, 49 % who continued after 16 weeks of tivozanib remained progression-free compared to 21 % who received placebo. The ORR for the entire period of the study with tivozanib was 24 % and the median PFS was 11.7 months in all study population. Hypertension was the most common grade 3 and 4 adverse event reported [45]. The phase III TIVO-1 trial is a randomized, controlled, open-label study of tivozanib compared with sorafenib. The preliminary results of this phase III trial were presented at the 2012 ASCO meeting. Tivozanib showed significant improvement in PFS and ORR as a first-line targeted agent compared with sorafenib in advanced RCC. In the study, 571 patients were randomized to two groups, tivozanib vs sorafenib. Median PFS for tivozanib and sorafenib were 11.9 and 9.1 months, respectively. ORR was 33 % in the tivazonib group and 23 % in the sorafenib group, but overall survival is not yet available. Adverse events reported with tivazonib were diarrhea, fatigue, neutropenia, hand–foot syndrome, and most commonly hypertension [46]. This phase III trial is estimated to be completed for primary outcome measurements in June 2013 [47].

Cabozantinib (XL-184) is another promising TKI for mRCC approved by the FDA in 2012 for medullary thyroid cancer treatment. It targets multiple tyrosine kinase receptors (VEGFR-2, MET, KIT, and RET) inhibiting angiogenesis as well as tumor growth [48]. A phase I drug–drug interaction study of cabozantinib–rosiglitazone in patients with solid tumors led to further evaluation of cabozantinib efficacy in patients with mRCC. All 25 patients with mRCC enrolled in the study had previously been treated with at least one or two lines of systemic therapy; 88 % had received prior anti-VEGF therapies. Out of 25 patients in the study, 7 (28 %) had ORR, 13 (52 %) had stable disease (SD), and 1 (4 %) had progressive disease (PD). Disease control rate (PR+SD) at 16 weeks was 72 %. Median PFS was 14.7 months (95 % CI, 7.3 months, upper limit not yet reached). Median OS was not yet reached. Three of four patients with bone metastases experienced a response. The most common grade 3 or 4 toxicities reported from this phase II study were hypophosphatemia (36 %), hyponatremia (20 %), and fatigue (16 %) [48, 49]. A randomized phase III trial of cabozantinib vs everolimus in patients with advanced RCC who failed prior TKI therapy evaluating for primary end point of PFS is underway [50].

Cediranib (AZD-2171) is a highly potent oral VEGF signaling inhibitor with positive results in a phase II study. In the initial phase I study in combination with gefitinib in patients with advanced solid tumors, the combination therapy was well tolerated and shown to have antitumor activity [51]. A phase II randomized, double-blind study of cediranib vs placebo in advanced RCC showed reduced tumor size from baseline (−20 %) in patients who received cediranib vs (+20 %) that in those who received placebo. Out of 53 patients treated with cediranib, 18 (34 %) had PR and 25(47 %) had SD. Median PFS was prolonged to 12.1 months in the treatment group vs only 2.8 months in the placebo group. The most common adverse events reported were diarrhea, hypertension, fatigue, and dysphonia [52].

Regorafenib (BAY 73–4506) is an oral antiangiogenic TKI recently approved by the FDA for advanced colon cancer treatment. It has been studied as a first-line treatment for mRCC or unresectable RCC in a single-group phase II trial. Out of 48 patients evaluated for tumor response, 19 patients experienced PR, 20 had SD, and 5 had PD. Four patients could not be assessed for response. Median PFS was 11 months. Grade 3 and 4 drug-related adverse events included hand/foot syndrome, diarrhea, renal failure, fatigue, hypertension, and cardiac ischemia. Two deaths likely related to treatment were reported [53].

Linifanib (ABT-869) is an oral TKI that recently completed phase II study. It was initially studied in refractory solid tumors in phase I, and it showed antiangiogenic activity in a biomarker study. In the study, 3 out of 33 patients had PR and 16 patients had SD for more than 4 cycles. A dose of less than or equal to 0.25 mg/kg/day was shown to be tolerable, and the reported adverse events were fatigue, proteinuria, hypertension, asthenia, hand and foot blisters, and myalgia [54]. A phase II study in patients with advanced RCC after sunitinib failure showed some activity. Out of 53 patients in the study, 13.2 % had ORR. The median PFS and time to progression were both 5.4 months and the median OS was 14.5 months. Significant dose modification of phase I trial dose was required in phase II to adjust for adverse events, and further studies for fixed dosing are required [55].

Conclusion

Since 2005, there has been a proliferation of targeted agents approved for advanced RCC. Two important clinical targets in VEGF and mTOR have emerged as effective molecules for inhibition. Pazopanib and axitinib are two new drugs approved for advanced RCC in the front-line and second-line setting after prior TKI therapy, respectively. Temsirolimus and everolimus are approved for metastatic RCC for poor-prognosis patients firstly and secondarily after prior TKI therapy, respectively. These drugs have increased the armamentarium for treatment of advanced RCC and are becoming pervasive in clinical practice. Furthermore, these targets are being explored with new drugs in clinical trials currently. Important questions remain including sequencing,

combination efficacy and toxicity, and predictive factors for response being explored in clinical trials.

Conflict of interest There are no potential conflicts of interest for the authors involved in this review paper.

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