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Comparison of small molecules VEGFR inhibitors in the treatment of renal cell carcinoma

Jie Yi Tan, Aadya Jaipuria, Ronny Priefer*
Massachusetts College of Pharmacy and Health Sciences University
179 Longwood Ave, Boston, MA 02115, USA

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ABSTRACT

Vascular endothelial growth factors receptors (VEGFR) inhibitors play a vital role in the treatment of renal cell carcinoma. These are small molecules that predominantly exhibit anti-angiogenesis activity in conjunction with other anti-tumor effects. These drug therapies are approved for the use in patients as frontline agents or adjuvant therapy in renal cell carcinoma. However, VEGFR inhibitors are associated with undesirable adverse events, with some having a more manageable toxicity profile compared to others. As a result, choice of treatment poses a challenge for healthcare providers and patients. Nonetheless, these agents demonstrate improved disease/progression free survival (DFS/PFS) values and remain a critical component in the treatment of kidney cancer.

Keywords: VEGFR inhibitors, renal cell carcinoma, kidney cancer, progression-free survival, adverse drug events

Corresponding author:
Ronny Priefer
Massachusetts College of Pharmacy and Health Sciences University
179 Longwood Ave, Boston, MA 02115, USA
Email: ronny.priefer@mcphs.edu

INTRODUCTION

Renal cell carcinoma is one of the most common types of cancer to be diagnosed. It ranks seventh among men and tenth among women, with an annual incidence of 63,000 and mortality of 14,000 deaths in the United States of America (Umeyama et al., 2017). The most common histologic subtype of kidney cancer is renal cell carcinoma which makes up ~90 % of all cases (Sneed et al., 2019). Additionally, the five-year survival rate is relatively low, at less than 20% (Staehler et al., 2021). Renal cell carcinoma is typically caused by a mutation in the von Hippel-Lindau (VHL) gene, a tumor suppressor gene that causes an accumulation of hypoxia inducible factors-1 (HIF-1) and, as a result, an overexpression of the vascular endothelial growth factor (VEGF), which promotes angiogenesis and cancer cell growth (Yalcin & Lacin, 2019). As a result, therapies that target VEGF receptors (VEGFR) are among the most popular and effective options for treating renal cell carcinoma. This inhibits downstream intracellular responses, resulting in decreased cell proliferation and, eventually, angiogenesis.

As of now, the FDA has approved six stand-alone small molecules that target VEGFRs as treatment options for renal cell carcinoma: pazopanib, sunitinib, sorafenib, tivozanib, cabozantinib, and axitinib. Furthermore, lenvatinib was only approved for use in conjunction with everolimus (an mTOR inhibitor). While all of these drugs are VEGFR inhibitors, the majority of them are also multi-targeting tyrosine kinase inhibitors. Only axitinib targets VEGFR 1, 2, and 3, making it the most selective and powerful inhibitor (Hutson et al., 2017). Conversely, sorafenib targets VEGFR-2, VEGFR-3, PDGFR-B, Flt3, c-KIT and p38-alpha, Raf-1 (c-Raf), and B-Raf activity. Currently, sunitinib and pazopanib are preferred first-line treatment options in renal cell carcinoma (Takyar et al., 2016).

Furthermore, despite having a similar mechanism of action in terms of anti-angiogenesis activity, these six small molecule drugs have different progression-free survival (PFS) values in both first-line and second-line therapy. Additionally, specific VEGFR inhibitors have higher PFS values or more severe adverse drug events in certain patient demographics. Moreover, treatment outcomes are determined by the patient's Memorial Sloan Kettering Cancer Center (MSKCC) performance status, which is classified as favorable, intermediate, or poor risk; however, this classification is not always applied consistently. The following is a review of the six previously mentioned VEGFR inhibitors, with emphasis on their reported benefits and drawbacks Table 1.

MATERIALS AND METHOD

Articles were collected with the aim of comparing the efficacy of the six FDA-approved VEGFR inhibitors for the treatment of renal cell carcinoma. Search terms utilized were: “renal cell carcinoma”, “kidney neoplasms”, “protein kinase inhibitor”, and “drug therapy” leading to 145 articles from 2011-2021 on PubMed. Analyzing these articles yielded summaries of the six VEGFR inhibitors; specifically, pazopanib, sunitinib, sorafenib, tivozanib, cabozantinib and axitinib Table 1.

Pazopanib

Pazopanib (Votrient), developed by Novartis, is an oral angiogenesis inhibitor which targets VEGFR 1, 2 and 3, PDGFR alpha and beta, fibroblast growth factor receptors 1 and 3, c-KIT, ITK, Lck, and c-Fms (Sternberg, 2010). It received FDA approval in 2009 and served as a first-line treatment for renal cell carcinoma after studies demonstrated its clinical efficacy and an improved progression free survival (PFS) value in patients (Motzer, 2017; Sternberg, 2013).A study conducted between 2011 and 2016 looked at 156 patients in Latin America (Brazil, Argentina, Colombia, Chile, and Mexico) with a mean age of 61.6 years, 73.7% male, and 51.3% Hispanic. 60.9% of these patients were diagnosed with stage IV renal cell carcinoma. However, among the participants, 81.3% discontinued treatment, with diarrhea, asthenia/fatigue, and nausea accounting for 51% of the reasons. Only 16.7% (n = 26) of patients stayed on pazopanib for the duration of the study. The investigator-assessed PFS in the Phase III COM-PAZ trial (10.5 months) and the global prospective observational PRINCIPLE study (10.3 months) were both 10.8 months (Fusco et al., 2017; Grünwald, 2016; Motzer et al., 2013).

Table 1. Description of the six VEGFR inhibitors

VEGFR Inhibitors	Mechanism of Action
Pazopanib:	Angiogenesis inhibitor of VEGFR 1, 2 and 3, PDGFR alpha and beta, fibroblast growth factor 1 and 3 receptors, c-KIT, ITK, Lck, and c-Fms
Sunitinib	Multi-tyrosine kinase inhibitor (RTK) of VEGFR 1,2 and 3, PDGFR alpha and beta, KIT, FLT3, CSF-1R, and RET
Sorafenib	Multi-tyrosine kinase inhibitor of Raf kinases, specifically Raf-1 (c-Raf), wild type, and mutant (V599E) B-raf activity
Tivozanib	Extremely potent selective tyrosine kinase inhibitor (TKI) of VEGFR 1,2, and 3, c-KIT and PDGFR-beta
Cabozantinib	Tyrosine kinase inhibitor of VEGFR 1,2 and 3, RET, MET, KIT, TRKB, FLT-3, AXL, ROS1, TYRO3, MER, and TIE 2; activity against tumor growth, metastasis, angiogenesis, and drug resistance.
Axitinib	Tyrosine kinase inhibitor that selectively targets VEGF-R 1, 2 and 3

Another study looked at pazopanib as a first-line treatment therapy in high-risk patients. From 2012 to 2016, 60 patients were enrolled in a "FLIPPER" trial at six sites across Germany to assess the efficacy and safety of pazopanib. The median age of the enrolled patients was 66, with men accounting for 79.1%. Patients were given 800 mg of pazopanib daily until disease progression, unacceptable toxicity, or the development of a second malignancy necessitating withdrawal and administration of another treatment were observed. Tumor response assessments were carried out every 8 weeks for a total of 6 months. As the study progressed, only 43 of the 60 patients were deemed eligible for further research. Similar to the aforementioned studies, patients enrolled experienced adverse drug reactions such as hypothyroidism (30.2%), diarrhea (25.6%), fatigue (18.6%), and nausea (11.6%). The median PFS was calculated to be only 4.5 months, notably lower than 10.5 that was reported in prior studies (Queiroz Muniz et al., 2019). A small sample size or a high proportion of immediate-risk patients could have contributed to the lowering of PFS value. In addition, the data only utilized descriptive statistics and no subgroup or explorations were conducted, thus the interpretation of results may be impeded by the single arm setting of the study (Staehler et al., 2021).

Moreover, additional studies found related results with PFS values closer to 10.5. From 2016 to 2018, the “Principal”, a prospective, observational study on pazopanib, was conducted in a multinational, real-world clinical setting, which enrolled 657 patients with a median age of 66, of which 68% (n=447) of whom were male. Data was collected from two groups of patients receiving pazopanib, classified as clinical trial eligible (CTE) and non-clinical trial eligible (NCTE) (14.8% vs 85.2%). The tumor responses were assessed according to physician’s clinical judgement every 3 months. The favorable/intermediate/poor risk for the two groups were 7.2/75.3/11.3% and 3.2/51.8/14.3%, respectively. In total, 501 (76.3%) of the 657 patients completed the study of a once daily pazopanib dose of 800mg. Similar efficacy was demonstrated for both groups CTE and NTCE using pazapanib, with PFS values of 9.6 and 10.7, respectively (Schmidinger et al., 2019).

Likewise, a single-arm, open-label, multicentered, Phase II clinical study conducted in Seoul, Korea with 29 patients receiving 800mg of pazopanib daily for renal cell carcinoma illustrated similar efficacy. The median age of enrolled patients was 58, with 72% (n=21) being male. Twenty-one (72%) patients were classified as MSKCC favorable risk, six (21%) as intermediate, and two (7%) as poor. During the follow-up period of 21.3 months, only 17 patients remained in the study, with 12 patients passing away due to disease progression. Nevertheless, the data collected from these 17 patients exhibited outstanding clinical efficacy with a PFS value of 16.5 months. Some key limitations in this study include the small population size and all patients were classified as either favorable (72%) or intermediate (28%) risk groups. These factors could have contributed to the clinical efficacy. Lastly, similar to the previously mentioned studies, 97% (n=28) of patients experienced one or more adverse drugs events: hypertension (66%), nausea/vomiting (59%), hair color changes (59%), diarrhea (55%), anorexia (48%), mucositis (45%), and abdominal pain (41%). All adverse events were deemed manageable (Jung et al., 2018).

Numerous other studies have illustrated clinical efficacy of pazopanib with PFS values of 8.1, 9.2 , 12.9, 13.1, or 15.9 (Poprach et al., 2018; Motzer et al., 2017; Okamura et al., 2019; Sneed et al., 2019;

Sternberg et al., 2010, 2013, 2014; Takahashi & Shibuya, 2005). The median age of patients from these studies ranges from 58-78 years old and the majority of patients were male.

Sunitinib

Sunitinib malate, (Sutent) was developed by Pfizer, and is an oral small molecule multi-tyrosine kinase inhibitor (RTK) that targets VEGFR 1,2 and 3, PDGFR alpha and beta, KIT, FLT3, CSF-1R, and RET. Inhibiting these RTK receptors exhibit potent antiangiogenic and antitumor activity. Sunitinib was approved in 2006 as a first line treatment and in 2017 as adjuvant therapy for patients at high-risk of recurring renal cell carcinoma. Various studies have illustrated the clinical efficacy of sunitinib, with significantly improved disease-free survival in both first line and adjuvant treatments, and increase patients' quality of life (Staehler et al., 2018). In addition, patients on Sunitinib were able to remain on treatment for a longer period due to manageable toxicity (Coelho et al., 2016).

A recent retrospective analysis looked at 1059 patients treated with sunitinib for renal cell carcinoma to investigate the prognostic factors for PFS. Sunitinib was administered as a first line (n=783,74%) or cytokine-refractory agent (n=276, 26%) in patients with a median age of 60, of which 70% were male, 83% were white, 7% were Asian, and 6% were non-white and non-Asian. The median PFS values were 9.7 and 23.4 months for first line and cytokine refractory, respectively. White patients were older and had higher rates of prior nephrectomy (83% vs 68%) and cytokine use (25% vs 14%) when compared with the other patient populations. There were no statistically significant differences in PFS between white and Asian patients. However, superiority was demonstrated over non-white, non-Asian patients (10.5 vs 6.6). Furthermore, as compared to Asian patients, the white patients were more like to experience adverse effects like nausea (55% vs 40%), dysgeusia (41% vs 26%), and decreased appetite (36% vs 17%) but, the Asian patients were more susceptible to hand-foot syndrome (70% vs 28%) and mucosal inflammation (40% vs 26%) (Motzer et al., 2013).

Another retrospective, longitudinal cohort study included 161 patients from cancer centers affiliated with the International Metastatic RCC Database (IMDC) in Belgium, Canada, Denmark, and the United States. With a median age of 63, the patient population consists of 125 men (78%) and 36 women (22%). Patients were divided into two groups based on how long they had been taking sunitinib: > 6 months (n = 116) and 6 months (n = 45), with a median duration of 11 months. Patients who had received first-line sunitinib treatment for more than six months underwent nephrectomy and had a lower IMDC risk at the start of sunitinib treatment than patients who had received less than six months of treatment. Only 32 patients remained on treatment, with 129 discontinuing due to disease progression (62%), toxicity (11%), or other reasons (6%). Patients who received more than 6 months of treatment had a longer median overall survival (OS) than those who received less (24.9 vs 17.5 months). The PFS value was difficult to calculate because many patients received and benefited from second and third-line therapies after experiencing adverse events (Wells et al., 2020).

A randomized, open-label, Phase 3 trial compared the efficacy and safety of pazopanib and sunitinib as first-line therapies in patients with renal cell carcinoma. A total of 1110 patients were enrolled to receive either pazopanib 800mg once daily (n= 557 patients) or sunitinib 50mg once daily for 4 weeks, followed by 2 weeks without treatment (n= 553 patients). Based on the severity of adverse events, doses were reduced to 600mg and 400mg for pazopanib, and 37.5mg and 25mg for sunitinib. Only 12% (n=68) and 6.3% (n=35) remained on the pazopanib and sunitinib, respectively at the conclusion of the study. Adverse events were observed in both groups, with sunitinib patients experiencing a higher incidence of fatigue (63% vs. 55%), hand-foot syndrome (50% vs. 29%), and thrombocytopenia (78% vs. 41%). The median PFS values for pazopanib and sunitinib were 8.4 and 9.5 months, respectively, demonstrating that pazopanib did not perform significantly worse than sunitinib. Pazopanib, on the other hand, was preferred over sunitinib in treatment due to its more manageable side effects and quality-of-life profile (Motzer et al., 2013).

A year-long randomized trial called "ASSURE" enrolled 358 patients (n=243 [67.9%] men, n=115 [32.1%] women) to receive sunitinib 50mg once daily and 356 patients (254 [71.3%] men, 102 [28.7%]

women) to receive placebo as adjuvant therapy. The average ages were 56.8 and 57.5 years old, respectively. This study looked at disease-free survival (DFS) in a subset of high-risk patients with clear cell histology, pT3, pT4, and/or node-positive disease. DFS was defined as the time between the start of sunitinib and the recurrence of renal cell carcinoma, the development of a second primary cancer, or death. The 5-year DFS rates for sunitinib and placebo were 47.7% and 50%, respectively, indicating that there is no clear rationale for sunitinib use in adjuvant therapy (Abdelaziz & Vaishampayan, 2017).

In contrast, the "S-TRAC" clinical trial compared the efficacy of sunitinib to placebo in a prospective, international, multicenter, randomized, double-blind Phase III trial. A total of 610 patients with a high risk of recurrence after nephrectomy were enrolled in the study and randomly assigned to receive sunitinib 50mg daily (n=304) or placebo (n=306). The EORTC QLQ-C30, a questionnaire designed to assess cancer patients' quality of life, was used to assess the patients' experiences every six weeks during treatment. In the sunitinib arm, 71% of patients (n=217) completed the study, while 29% (n=177) dropped out due to adverse events of which diarrhea (56.9%), palmar-plantar erythrodysesthesia (50.3%), and hypertension (36.9%) were the most common. However, these adverse events typically resolved within 3.5 weeks. The analysis of patient reported outcomes did not show any clinically meaningful deterioration in most measures of quality of life and in their global health status. Additionally, the trial demonstrated a statistically significant and clinically meaningful 24% reduction in the risk of occurrence of a DFS event versus placebo, 6.8 vs 5.6 years, respectively (Staehler et al., 2018).

Sorafenib

Sorafenib (Nexavar), developed by Bayer Healthcare Pharmaceuticals, is a multi-tyrosine kinase inhibitor which targets Raf kinases, specifically Raf-1 (c-Raf), wild type, and mutant (V599E) B-raf activity that mediates cell proliferation, differentiation, and transformation. In addition, sorafenib also targets VEGFR-2, VEGFR-3, PDGFR-B, Flt3, c-KIT, and p38-alpha, regulating the activity of endothelial apoptosis and angiogenesis (Huang, 2019). In December 2005, sorafenib was approved by the FDA as a second line therapy for renal cell carcinoma, despite all the controversies about its therapeutic benefits.

SORCE, an international, randomized, double-blinded, three-armed, Phase III clinical trial evaluated the different durations of adjuvant sorafenib compared to placebo. The study included 1,711 patients with a median age of 58 years, 71% of whom were male and had clear cell histology, 53% of whom were at intermediate risk, and 47% of whom were at high risk of recurrence. Participants were divided into three groups at random (430, 642, and 639 in arms A, B, and C, respectively). Arm A received three years of placebo; Arm B received one year of sorafenib followed by two years of placebo; and Arm C received three years of sorafenib. Patients were initially given a 400mg dose of sorafenib, which could be maintained or increased to the total dose of 400mg twice daily after three weeks of treatment due to higher-than-expected discontinuation rates. Patients were followed up after three, six, and twelve weeks. Rash, fatigue, diarrhea, hand-foot syndrome, nausea, hypertension, and alopecia are among the side effects reported in 366 patients (58.6%) who received 1 year of sorafenib, 392 patients (63.9%) who received 3 years of sorafenib, and 124 patients (29.2%) who received placebo. Finally, no differences in DFS or OS were observed in all randomly assigned patients. Sorafenib was deemed ineffective for adjuvant therapy in patients with resected RCC who were at intermediate or high risk of relapse (Haas et al., 2016).

Additionally, a multicentered, retrospective study was conducted in Northwestern China on 96 patients, where 48 participants received 400mg of sorafenib twice daily for three months and 48 received placebo. The median age of the patient population was 50, 78% male (n=75), and 93.75% (n=45) belonged to the Han ethnic group. All patients had previously underwent tumor resection and were followed up every 6 months. Similar adverse events were reported in the aforementioned study. Kaplan-Meier plot was used to determine the DFS values between sorafenib and placebo treated groups, with no significant difference observed (Wei et al., 2019).

In contrast, a large-scale prospective registration study in Japanese patients looked at the use of sorafenib to assess real-life safety and efficacy in advanced renal cell carcinoma. The study enrolled 3255 patients, with a median age of 67, a male gender ratio of 75.3% (n= 2450), and a median weight of 58.5kg. Sorafenib (800mg) was given to patients daily for a median of 6.7 months. At the end of the 12-month study, only 1028 (31.6%) patients remained on treatment. In total, 2227 patients stopped taking their medications due to adverse events (52%), ineffectiveness (31.3%), or other reasons (16.7%). The median PFS was 7.3 months (95% confidence interval [CI]: 6.7-8.1), with a 1-year OS rate of 75.4% (73.5-77.1). The PFS value was consistent with those in previous clinical trials in the multivariate analysis, demonstrating meaningful clinical efficacy of the use of sorafenib for renal cell carcinoma (Akaza et al., 2015).

A double-blind, placebo-controlled, randomized Phase III trial compared the benefits of sunitinib and sorafenib on patients at high risk of recurrence after nephrotomy. In total, 1943 treatment-naive patients from 225 study sites in the United States and Canada were enrolled. For a total of 54 weeks, patients were randomly assigned to receive a daily dose of 50mg sunitinib (n=647), 400mg twice daily sorafenib (n=649), or placebo (n=647). When toxicities were discovered, doses were reduced to 37.5 mg for sunitinib and 400 mg for sorafenib. Patients were assessed every six weeks in the first three cycles, followed up every six months for two years, and then once per year for ten years. Similar to the aforementioned studies, the most common grade adverse events were hypertension (n=105 [17%] sunitinib vs n=102 [16%] sorafenib), hand-foot syndrome (n=94 [15%] sunitinib vs n=208 [33%] sorafenib), rash (n=15 [2%] sunitinib vs n= 95 [15%] sorafenib), and fatigue (n=110 [17%] sunitinib vs n=44 [7%] sorafenib) (Haas et al., 2016). The median DFS values were 5.8 for sunitinib, 6.1 years for sorafenib, and 6.6 years for placebo. The DFS values between these groups did not differ significantly, illustrating a lack of efficacy in therapeutic use for renal cell carcinoma (Haas et al., 2016).

Tivozanib

Tivozanib (Fotivda), developed by AVEO oncology, is an oral and extremely potent selective tyrosine kinase inhibitor (TKI) of VEGFR 1,2, and 3 as well as c-KIT and PDGFR-beta. Tivozanib allows inhibition of angiogenesis and reduction of regulatory T-cell production at low serum concentration. Tivozanib was approved by the FDA in March 2021 for the treatment of relapsed or refractory advanced renal cell carcinoma (Yalcin & Lacin, 2019).

A Phase II clinical trial in Europe enrolled 272 patients, 54% (n=147) of whom had not previously been treated with VEGF kinase inhibitors. All participants were given 1.5mg of tivozanib every day for three weeks, followed by a one-week break. Patients who experienced more than 25% tumor shrinkage or an increase in tumor size at 16 weeks were initially removed from the study. Patients who did not meet these two criteria were randomly assigned to either 12 weeks of tivozanib or placebo, with the option to continue with tivozanib until week 16. A total of 76 patients discontinued treatment, with disease progression accounting for 65% (n=50) and other reasons accounting for 34% (n=26). The overall median PFS values with tivozanib and placebo were 10.3 and 3.3 months, respectively. Hypertension (45%), dysphonia (22%), increased gamma-glutamyl transpeptidase (17%), diarrhea (12%), increased uric acid (7%), and hypokalemia (6%) were among the toxicities (Boyle, 2013).

An open-labeled, randomized Phase III trial compared tivozanib and sorafenib as initial targeted therapy in patients with renal cell carcinoma in Central or Eastern Europe. A total of 517 patients were enrolled in the study, with a mean age of 59 and 71% (n=185) being male. Patients were randomly assigned to either tivozanib (n=260) or sorafenib (n=257) for 12 months. Only 106 (41%) and 65 (25%) patients remained on tivozanib and sorafenib, respectively, at the time of analysis. The most common reasons for stopping treatment were disease progression (79% vs 79%), treatment-emergent adverse events (12% vs 9%), and death (4.6% vs 4.6%). The median PFS values for tivozanib and sorafenib were 11.9 and 9.1 months, respectively, indicating that tivozanib has some superior efficacy (Motzer et al., 2013). Additional studies have also compared tivozanib (n=260), versus sunitinib (n=375), and

pazopanib (n=290) with median PFS values of 11.9 (12.7 for treatment naive patients),11.0, and 9.2 months (11.2 for treatment naïve, 7.4 for cytokine pre-treated), respectively (Wong & Eisen, 2013).

Cabozantinib

Cabozantinib (Cabometyx), developed by Exelixis, is an oral tyrosine kinase inhibitor of VEGFR 1,2 and 3, RET, MET, KIT, TRKB, FLT-3, AXL, ROS1, TYRO3, MER, and TIE 2, with activity against tumor growth, metastasis, angiogenesis, and drug resistance. Cabozantinib was approved in 2016 for the treatment of advanced renal cell carcinoma in patients who had previously received antiangiogenic therapy (Singh et al., 2017). Various studies have demonstrated the clinical efficacy of cabozantinib with promising improved DFS as well as manageable toxicities.

In Poland, 115 patients who had relapsed after prior antiangiogenic therapy regimens were studied in a real-world retrospective study. The participants' average age was 64, and 84% (n=73) were male. 50% (n=57.5) of patients had bone metastases, 10% (n=11) had brain metastases, and 4.3% (n=5) had non-clear cell carcinoma and 76% (n=87) had received more than two lines of therapy. A daily dose of 60mg cabozantinib was administered to the patients During the median follow-up period of 12.5 months, 110 patients remained in the study, with only 5 patients discontinued due to adverse events such as fatigue (23%), diarrhea (10%), and hand-foot syndrome (12%). The median PFS value was 12.5 months, and 6, 12, and 18 months of OS rates were 85.6%, 70.4%, and 65.1%, respectively. The OS along with the PFS values for cabozantinib demonstrated clinical efficacy in renal cell carcinoma (Bodnar et al., 2019).

A multicentered, international, retrospective, cohort analysis looked at 112 patients with non-clear-cell renal cell carcinoma treated with cabozantinib 60 mg (reduced dose to 40mg when toxicities occurred) in the US (21 centers) and Belgium (1 center). The average age was 60, with 85 (76%) men and all with a performance status of 0-1. Only 38 patients (34%) remained on therapy after 11 months of follow-up, with 74 (66%) discontinuing treatment due to disease progression (n=63, 85%), adverse events (n=5, 7%), patient preference (n=2, 3%), physician preference (n=1, 1%), or other reasons (n=3. 4%). The median PFS value was 7 months, indicating that cabozantinib demonstrated promising antitumor activity (Martínez Chanzá et al., 2019).

A randomized, open-label phase III trial called "METEOR" enrolled 330 patients with advanced or metastatic renal cell carcinoma who had previously been treated with VEGFR tyrosine kinase inhibitors. 60mg Cabozatinib was administered once daily. The average age was 63, there were 253 (77%) men, and the median follow-up time period was 18.7 months. Only 73 (22% of patients) finished treatment, with 257 dropping out due to disease progression (48%, n=159), adverse events (12%, n=40), clinical deterioration (10%, n=35), or other reasons (n=23, 7%). Cabozantinib had a PFS of 7.4 months, indicating that it was clinically effective and helped to increase overall survival, improve objective response, and delay disease progression (Buti & Bersanelli, 2017).

A randomized, multicenter, Phase II "CABOSUN" clinical trial enrolled 157 patients, with a mean age of 63 and 78% (n=123) being male, to compare the benefits of cabozantinib versus sunitinib. Patients were at low or intermediate risk and had not previously been treated with other systemic agents. Candidates were randomly assigned to either a daily dose of 60mg cabozantinib (n=79) or a once-daily dose of 50mg sunitinib (n=78). The treatment was carried out in five cycles of six weeks each. Sunitinib, on the other hand, was only given for four weeks, followed by a two-week break. Diarrhea (10% vs 11%), fatigue (6% vs 15%), hypertension (28% vs 22%), and hand-foot syndrome (8% vs 4%) were all grade 3 or 4 adverse events reported in both cabozantinib and sunitinib patients (Choueiri et al., 2017).

Axitinib

Axitinib (Inlyta), developed by Pfizer, is an oral, potent tyrosine kinase inhibitor that selectively targets VEGF-R 1, 2 and 3 and establishes anti-angiogenic and anti-tumor activity (Akaza & Fukuyama, 2014). Axitinib was approved in January 2012 as an adjuvant therapy for renal cell carcinoma (Ornstein

et al., 2019). Various studies have illustrated clinical efficacy of axitinib, with improved progression free survival in second-line therapy.

A Phase III, randomized, double-blind "ATLAS" clinical trial enrolled 724 patients in France, India, Japan, Korea, Spain, and Taiwan, with more than half having clear-cell renal cell carcinoma and having undergone nephrectomy. Patients were randomly assigned to receive either 5mg axitinib twice daily (n=363) or placebo (n=361). The median age of the patients was 58, with 73% (n=146) being male. A total of 204 (57%) patients in the axitinib group and 176 (49%) patients in the placebo group discontinued treatment due to recurrence/secondary malignancy (15% vs 23%), adverse events (19% vs 5%), or patient consent withdrawal (13% vs 10%). No direct DFS values were obtained due to termination of the clinical trial because of a preplanned interim analysis, however, no significant difference in DFS per independent review committees (IRC) assessment in the ITT population was observed (Gross-Goupil et al., 2018).

To evaluate the efficacy of axitinib, a Phase II "AXIPAP" multicenter, open-label, single-arm study was conducted in France. Forty-four patients with group performance status 0 or 1, prior nephrectomy, and a mean age of 65 were enrolled to receive a twice-daily oral dose of 5mg axitinib. The median drug exposure time was 8 months, and the median follow-up time was 21 months. Only 21 patients remained in the study at the time of analysis, and the PFS value was 6.6 months, indicating encouraging efficacy, particularly in Type II papillary renal cell carcinoma (Negrier et al., 2020). Similar adverse events were seen in the aforementioned study (Gross-Goupil et al., 2018).

In addition, in Japan, a retrospective chart review was performed on patients who received a single oral dose of 10 mg axitinib as first-line therapy for renal cell carcinoma. A total of 38 patients were enrolled, with a median age of 66 and an 86.8% (n=33) male population. Most patients were classified as intermediate (n=15, 39.5%) or poor (n=16, 42.1%) IMDC risk. A median PFS of 12.8 months was found to be very encouraging. Similar adverse events were seen as aforementioned study (Gross-Goupil et al., 2018).

A systematic review of completed, randomized, controlled trials comparing the efficacy of axitinib, sorafenib, sunitinib, and pazopanib with a primary focus on their PFS values was published. The article discussed the use of TKIs as first-line therapy in patients with advanced renal cell carcinoma classified as locally advanced, metastatic, tumor, node, metastasis (TNM) stage III or IV who had not previously been treated with TKIs. The PFS values reported were 10.1 months [axitinib in the Hutson study]; 5.8, 5.7 6.5 and 9.1 months [sorafenib in the TARGET sub analysis, Escudier et al, Hutson et al, TIVO-1 study trials respectively]; and 11, 9.5, and 8.2 months [sunitinib in Motzer et al, COMPARZ, and TORAVA clinical trials respectively] (Takyar et al., 2016).

Table 2. Summary of the advantages and disadvantages of VEGFR inhibitors

Drugs	Advantages	Disadvantages
Panzopanib	• Improved progression free survival values of 10.5 and 16.5 months in Brazilians and Koreans • Once daily dosing of 800mg • Works well in MSKCC classified favorable to intermediate risk group	• Adverse drug events: hypothyroidism, diarrhea, fatigue, and nausea. • Insufficient progression free survival value of 4.5 months in Germans
Sunitinib	• Improved progression free survival value of 9.7 months for first line • No statiscally difference in progression free survival values found between White and Asian patients • Once daily dosing of 50mg • Dose reductions of 37.5 and 25mg available • Approved for both first line and adjuvant therapy • Manageable toxicities and retain quality of life • Low discontinuation rates due to adverse drug events	• Adjuvant therapy shows no improved progression free survival

Table 2. Summary of the advantages and disadvantages of VEGFR inhibitors (Continue)

Drugs	Advantages	Disadvantages
		• Adverse drug events: white patients experience in nausea, dysgeusia, and decreased appetite; Asian patients experience more hand-foot syndrome and mucosal inflammation
Sorafenib	• Beneficial progression free survival value in Japanese patients	• Twice daily dosing of 400mg • Adverse events include rash, fatigue, diarrhea, hand-foot syndrome, nausea, hypertension, and alopecia • Inefficient as adjuvant therapy for patients with resected renal cell carcinoma at intermediate or high-risk relapse • No clinical efficacy was found when compared to placebo and the American, Canadian, and Chinese population • Can only be used as adjuvant therapy
Tivozanib	• Once daily dosing of 1.5mg • Effective at very low drug serum concentration • Potent vascular endothelial growth factor receptors (VEGFR) tyrosine kinase • Clinical efficient progression free survival value of 10.3 months • Manageable toxicities • Low discontinuation rates due to adverse drug events • May be used in patient who have not received any antiangiogenic treatment prior	• Adverse drug events: hypertension, dysphonia, increased gamma-glutamyl transpeptidase, diarrhea, increased uric acid and hypokalemia.
Cabozantinib	• Once daily dosing of 60mg • Progression free survival value of 12.5 months with previously received more than 2 lines of therapy • Progression free survival value of 7 months in patients with performance status of 0-1, indicates encouraging antitumor activity • Low discontinuation rate that is due to adverse events 5-12%	• Adverse drug events: fatigue, diarrhea, and hand-foot syndrome • Can only be used as adjuvant therapy
Axitinib	• Potent and selective vascular endothelial growth factor receptors (VEGFR) inhibitor • Established improved progression free survival value • Encouraging efficacy of a progression free survival value of 6.6 months in type II papillary renal cell carcinoma in French patients • Strong progression free survival value of 12.8 months in intermediate and poor International Metastatic renal cell caricinoma Database Consortium (IMDC) risk group in Japanese populations	• Twice daily dosing of 5mg • Only approved as adjuvant therapy • Adverse drug events: Grade 3/4 adverse events included hypertension, diarrhea, dysphonia, hand-foot syndrome

Fusco, 2017; Motzer, 2015; Grunwald, 2016; Schmidinger, 2018; Jung, 2018; Motzer, 2013; Abdelaziz, 2017; Haas, 2016; Wei, 2019; Akaza, 2015; Boyle, 2013; Bodnar, 2019; Gross-Goupil, 2018; Negrier, 2020

CONCLUSION

VEGFRs inhibitors continue to serve a critical role in the treatment of renal cell carcinoma with six FDA approved drugs currently on the market. Of these, pazopanib and sunitinib are the only two that serve as first-line therapy with both demonstrating improved PFS values. Sunitinib has a lower therapy

discontinuation rate due to its more manageable toxicity profile as well as having the option to reduce drug dose. Sunitinib is also approved as an adjuvant therapy but has failed to demonstrate clinical efficacy as a second-line treatment.

Axitinib, cabozantinib, sorafenib, and tivozanib are all approved as adjunct therapy and have demonstrated clinical efficacy, with conflicting results related to sorafenib. Axitinib is the only selective VEGFRs inhibitor, possessing an excellent PFS value, however with a more severe toxicity profile. Tivozanib has demonstrated excellent PFS value and requires only a low drug serum concentration for the treatment of renal cell carcinoma. Additionally, tivozanib established a clinically significant PFS value in patients who have not been previously treated with anti-angiogenic agents, shifting its potential role to first-line therapy in the future. Finally, lenvatinib (a VEGFR inhibitor) in combination with everolimus (a mTOR kinase inhibitor) demonstrated promising clinically efficiency and has been administered to patients for the treatment of renal cell carcinoma. A summary of the advantages and disadvantages of the six VEGFR inhibitors is provided in Table 2.

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