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Target Therapy for Kidney Cancer

Yang Wang and Lingxiang Liu

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Abstract

Renal cell carcinoma (RCC) is considered a chemotherapy-resistant tumor; the landscape of metastatic RCC (mRCC) is rapidly changing due to the development of target therapy. By now, 10 novel agents have dramatically improved the prognosis of mRCC. The purpose of this chapter is to provide an updated overview of the clinical data, which support the use of these agents. We conducted a systematic review using PubMed and ClinicalTrials.gov about target therapy in RCC according to the existing guidelines, made analysis of the clinic trials, and discussed their mechanism, impact on quality of life (QoL), and patient selection algorithms. A total of 11 completed phase III trials were included in our research data. Agreement was correlated with the availability of data in seven trials, contributing to the category 1 option of first-line therapy for patients with mRCC. Three completed phase III trials contributed for the subsequent therapy as the evidence. Target therapy shows promise in clinical practice. Guidelines and algorithms should be revised and adapted to the new target drugs. However, more research is needed in parallel to discover biomarkers that enable the prediction of a treatment response and therefore lead to better patient selection.

Keywords: renal cell cancer, target therapy, tyrosine kinase inhibitor, immune checkpoint inhibitors, clinical trial

1. Introduction

About 25–30% of renal cell carcinoma patients are in locally advanced or metastatic stage when diagnosed, an additional third patients with localized tumor will recur after rational surgery. Before 2005, treatment option for advanced renal cell carcinoma (RCC) was limited to cytokines and clinical trial. With both IFN and IL-2, the response rate was only 5–27% [1, 2], while

associated with substantial side effect. The last decade witnessed the important advance in the development of renal cell carcinoma (RCC) molecular biology, which leads to the improvement in the survival of patients with advanced RCC, Nowadays, half of the patients with advance RCC are likely to survive more than 2 years. Currently, 10 targeted agents are approved for first-line or later-line use in the treatment of patients with RCC including one monoclonal antibody targeting vascular endothelial growth factor (VEGF; bevacizumab), six multi-targeted tyrosine kinase inhibitors (TKIs; sunitinib, sorafenib, axitinib, pazopanib, cabozantinib, and lenvatinib), two target the mammalian target of rapamycin (mTOR) pathway (everolimus and temsirolimus), and one target the immune checkpoint programmed death-1 (PD-1) pathway (nivolumab) (**Figure 1**). The guidelines of kidney cancer recommend first-line pazopanib, sunitinib, bevacizumab (plus interferon-2b [IFN-2b]) as category 1 recommended for patients with clear cell histology and good or intermediate Memorial Sloan Kettering Cancer Center (MSKCC) prognosis (NCCN category 1 preferred, European Society for Medical Oncology (ESMO) level I evidence of activity and grade A recommendation). Temsirolimus is only recommended as first-line treatment for poor-prognosis patients, and in the latest version of NCCN 2018, cabozantinib was added to the first-line therapy for poor- and intermediate-risk patients based on modified MSKCC criteria [3]. For patients who experience disease progression during (or who are intolerant to) treatment with a first-line target treatment, subsequent therapy with the highest level of evidence include cabozantinib, nivolumab, axitinib, or lenvatinib plus everolimus. Although several targeted agents were recommended, the optimal sequence has not been determined. The goal of therapy for patients with mRCC is to prolong survival while maintaining good quality of life, which should be taken into consideration when choosing second-line and third-line agents. Choosing a sequence of targeted agents with nonoverlapping safety profiles might improve quality of life by improving tolerability. Looking forward, identification of the optimal sequence of targeted agents might be achieved through identification of biomarkers and individualization of treatment for patients with mRCC.

Prognostic scoring systems used in some clinical trials is from the Memorial Sloan Kettering Cancer Center (MSKCC), which was derived from evaluating prognostic factors in patients with mRCC in clinical trials [4]. The validated MSKCC model includes the following five independent predictors of short survival: time from diagnosis to treatment less than 1 year; Karnofsky performance status less than 80%; lactate dehydrogenase level more than 1.5 times ULN; low serum hemoglobin level, and corrected serum calcium level more than 10 mg/dL). Patients with 0, 1–2, or 3 risk factors are stratified into categories as low risk with good
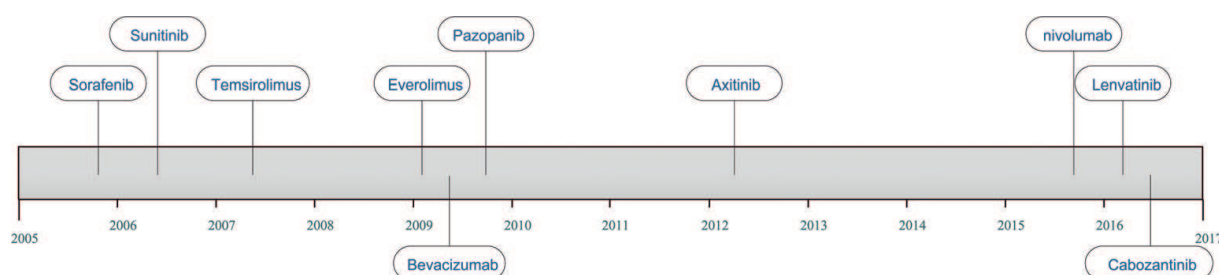

Figure 1. Chronological transition of pharmacotherapy for mRCC in USA.

prognosis, intermediate risk, or poor risk, respectively. The MSKCC model has been validated by an independent group at the Cleveland Clinic, and has been valuable in identifying the most effective treatment strategy [5].

2. Approved drugs

2.1. Targeting VEGF/VEGFR

Angiogenesis is a key target in the treatment of advanced RCC. Therapeutic strategies include the inhibition of the receptor of the vascular endothelial growth factor (VEGFR) by tyrosine kinase inhibitors and the blockage of the ligand (VEGF) by monoclonal antibodies.

2.1.1. Sorafenib

Sorafenib is a small molecule multi-tyrosine kinase inhibitor that targets RAF, MEK, ERK, VEGFR1–3, PDGFR-β, c-KIT, RET, CRAF, and BRAF, which are involved in tumor cell proliferation and angiogenesis [6].

A randomized phase II trial investigated the efficacy and safety of sorafenib vs. IFN-2α in previously untreated patients with clear cell RCC. One hundred and eighty nine patients were randomized to receive oral sorafenib (400 mg twice daily) or subcutaneous IFN-2α. When the disease progressed, the dose of sorafenib escalated to 600 mg twice daily for sorafenib patients and IFN-2α patients had to crossover to sorafenib (400 mg twice daily). The primary endpoint was PFS.

Ninety seven patients in the sorafenib arm received treatment and had a median of 5.7 months PFS vs. 5.6 months for IFN-2α. More sorafenib-treated patients had tumor regression (68.2 vs. 39.0%). Overall, sorafenib-treated patients show fewer symptoms and better quality of life [7].

The clinical efficacy of sorafenib has also been shown in the phase III randomized TARGET trial [8, 9]. Nine hundred and five cytokine-refractory mRCC patients with favorable or intermediate MSKCC risk were randomly assigned to receive sorafenib vs. placebo. The median PFS was longer in the experimental arm at the time of the interim analysis (5.5 vs. 2.8 months; hazard ratio (HR) 0.44; p < 0.01) and a median overall survival (OS) of 17.8 months, which was statistically identical with that of the placebo group, 15.2 months. The most common grade 3 or 4 adverse events (AEs) sorafenib was associated with were as follows: hand-foot-syndrome (86%), fatigue (5%), dyspnea (4%), and hypertension (4%).

Sorafenib was approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in December 2005 and July 2006, respectively. It was listed as a category 2A option as first-line treatment for patients with relapse or unresectable stage IV predominantly clear cell renal carcinoma.

In second line, efficacy of sorafenib was studied in patients who progressed to a previous tyrosine kinase inhibitor (TKI). The international phase III trial INTORSECT [10] randomized

512 mRCC patients with progressive disease after sunitinib in two groups: temsirolimus 25 mg once weekly (n = 259) or sorafenib 400 mg twice a day (n = 253). The median PFS did not differ statistically (4.2 vs. 3.9 months) but the secondary endpoint, the OS, favored sorafenib (12.3 vs. 16.6 months).

Sorafenib has also been evaluated in the adjuvant therapy in ASSURE trial [11], however, no clinical benefit both in the PFS and OS was showed compared to placebo. There are still several clinical trials that are ongoing in order to verify the role of sorafenib in the adjuvant setting of RCC, the SORCE trial compares sorafenib to placebo for 1 or 3 years after surgery (NCT00492258) and The RESORT trial is assessing the clinical value of sorafenib for 1 year after radical resection of the metastases (NCT01444807) [12].

2.1.2. Sunitinib

Sunitinib is an oral multikinase inhibitor that targets VEGFR 1–3, c-Kit, PDGFR, FMS-like tyrosine kinase-3 (Flt3), and neurotrophic factor receptor (RET). A large multinational phase III trial compared sunitinib vs. IFN in 750 untreated patients with mRCC. Patients selected for the trial had no prior treatment, and around 90% of the patients in the trial had either favorable or intermediate MSKCC risk features. They were randomized 1:1 to receive oral sunitinib or subcutaneous IFN. This trial showed a statistically significant benefit for experimental arm in both objective response rate (ORR) (39 vs. 6%; $p < 0.001$) and median PFS (11 vs. 5 months; HR 0.54; $p < 0.001$). However, no difference in median OS was seen, maybe it is due to the crossover occurring in more than 50% of placebo-assigned patients. The most common grade 3–4 adverse events (AEs) reported were neutropenia (12%), thrombocytopenia (8%), hypertension (8%), hyperamylasemia (5%), hand foot syndrome (5%), and diarrhea (5%) [13]. Updated results of the trial demonstrate a strong trend toward median OS in the sunitinib group than in the IFN-α group (26.4 vs. 21.8 months, p = 0.051) [14].

Based on these studies, this drug received full approval in February 2007 from both the FDA and the EMA due to the study findings in untreated patients with advanced RCC. And the NCCN Kidney Cancer Panel has also listed sunitinib as a preferred category 1 option for first-line treatment for patients with relapsed or medically unresectable predominantly clear cell stage IV renal carcinoma.

Sunitinib also has demonstrated substantial anti-tumor activity in the subsequent-line therapy of metastatic RCC after progression on cytokine therapy [15, 16]. Studies investigating the sequential use of sunitinib and sorafenib are mostly retrospective, along with limited prospective data, showing their differences in target specificities and slightly different toxicity spectra that sometimes permit tolerance of one agent over another [17–19]. Sunitinib is considered a category 2A subsequent therapy option and was registered by the FDA in January 2006 for patients with mRCC refractory to cytokine therapy.

2.1.3. Pazopanib

Pazopanib is an oral second-generation multitarget receptor tyrosine kinase inhibitor that targets VEGFR1–3, PDGFR, and c-Kit [20].

The safety and efficacy of pazopanib was evaluated in a double blind, phase III, international study. Four hundred and thirty five patients with locally advance and/or mRCC were enrolled with no prior treatment or with one prior cytokine-based treatment. All the patients were randomized 2:1 to pazopanib 800 mg daily or placebo. Pazopanib was significantly associated with a longer median PFS compared with the placebo arm (9.2 vs. 4.2 months; $p < 0.0001$) [21]. And in the treatment-naive subgroup of 233 patients, pazopanib arm also showed survival advantage with median PFS of 11.1 months vs. 2.8 months on placebo. The ORR was 30% with pazopanib and 3% with placebo. The most common grade 3/4 AEs related to pazopanib was hypertension and diarrhea. The most common grade 3/4 chemistry abnormalities were ALT elevation and AST elevation.

Another phase III noninferiority study (COMPARZ) compared randomly pazopanib to sunitinib as first-line therapy for advanced RCC [22], the PFS being the primary endpoint. One thousand one hundred and ten patients with mRCC were randomized to receive pazopanib or sunitinib. The predefined criterion for noninferiority was reached with a median PFS of 8.4 and 9.5 months for pazopanib arm and sunitinib arm respectively (HR 1.05; 95% CI 0.90–1.22), and ORRs were 31% for pazopanib, and 25% for sunitinib. This trial showed a different safety profile between both drugs: diarrhea and hepatotoxicity being more frequent with pazopanib, while fatigue, hand-foot syndrome, and alteration in taste were most seen with sunitinib.

Based on the above evidence, Pazopanib was approved as first-line therapy by the FDA for the treatment of advanced/metastatic RCC in 2009. And the NCCN Kidney Cancer Panel has listed pazopanib as a preferred category 1 option for first-line treatment of patients with relapsed or medically unresectable predominantly clear cell stage IV renal carcinoma.

2.1.4. Axitinib

Axitinib is a second-generation multitarget TKI that inhibits the receptors VEGFR1–3 and with low inhibitory activities against PDGFR-α, $-\beta$ and c-Kit.

Some preclinical and clinical data suggested that axitinib might have an increased efficacy when compared with first-line VEGFR inhibitors. Two phase II trials evaluated axitinib in patients with cytokine refractory mRCC after sorafenib, the ORR reached 44 and 22.6%, respectively. The phase III AXIS trial compared axitinib and sorafenib in the second-line therapy of mRCC, 723 patients in 22 countries were enrolled in the trial. Patients who had progressed after an initial systemic therapy including sunitinib (54%), cytokines (35%), and bevacizumab-IFN or temsirolimus (11%) were randomized to 1:1 to axitinib 5 mg twice daily and sorafenib 400 mg twice daily as a second-line option. Dose of axitinib was predefined to escalate to 10 mg twice daily according to the toxicity profile of each patient. PFS was the primary endpoint, patients in the axitinib group showed significantly longer PFS than in the sorafenib group (6.7 vs. 4.7 months; HR 0.67; $p < 0.001$). The type of prior treatment did not impact those study findings. The ORR differed significantly in both arms (19.4 vs. 9.4%; $p < 0.001$). The most common adverse events were diarrhea (55%), hypertension (40%), and fatigue (39%) in the axitinib arm. However, the updated result showed no difference in the terms of OS between the two groups (20.1 vs. 19.2 months, $p = 0.3744$) [23].

To determine its effectiveness in the first-line setting, a randomized, phase III study was carried out. Around 288 patients were randomized 2:1 to receive axitinib and sorafenib, and the result indicated that axitinib was associated with improvements in both median PFS: 6.5 vs. 10.1 months (HR 0.767; p = 0.0377) and ORR 14.6 versus 32.3% (p = 0.0006), respectively, while these results were inferior to those of sunitinib or pazopanib [24].

Based on these results, the NCCN panel listed axitinib as a first-line treatment option (category 2A) and second-line treatment option (category 1).

Axitinib is also being evaluated in the adjuvant setting in the ATLAS trial (NCT01599754), a prospective, randomized, double blind placebo-controlled phase III trial, axitinib was given orally at 5 mg twice daily for 3 years vs. placebo. The study has completed recruitment and the results are awaited.

2.1.5. Lenvatinib

Lenvatinib is an oral active multikinase inhibitor that shows inhibitory activity against VEGFR1–3, FGFR 1–4, PDGFR-β, RET, and KIT.

A phase Ib clinical trial evidenced that the combination of daily lenvatinib 18 mg and everolimus at 5 mg was a potential therapeutic option for mRCC patients who had disease progression after antiangiogenics therapy: the OR was 30% and the median PFS reached 330 days (95%CI 157-446) [25].

A multicenter phase II trial that randomized 153 patients with metastatic, unresectable, or locally advanced mRCC whose disease progressed after a first-line treatment of anti-angiogenic agents. Patients were randomized to lenvatinib plus everolimus or single agent of lenvatinib or everolimus. Patients treated with the combination therapy experienced better PFS than patients treated by everolimus alone (14.6 vs. 5.5 months; HR, 0.40; 95% CI 0.24–0.68), and also with superiority in OS (25.5 vs. 15.4 months; HR, 0.67; 95% CI 0.42–1.08). Grade 3–4 AEs occur in fewer patients with everolimus alone compared with lenvatinib alone and combination therapy (everolimus 50%, lenvatinib 79%, combination 71%) [26].

In March 2016, the FDA approved the combination of lenvatinib with everolimus for the treatment of patients with advanced RCC following one prior antiangiogenic therapy, and it was listed as a category 1 recommendation for subsequent therapy by the NCCN Cancer Panel. In July 2016, the EMA registered the combination under accelerated assessment program.

2.1.6. Cabozantinib

Cabozantinib is an oral small molecule TKI of MET, VEGFR2, RET, and AXL with promising antitumor activity evidenced in preclinical studies. The clinical effectiveness of cabozantinib focused in patients who had already progressed to previous treatment. METEOR is a randomized open-label phase III clinical trial, which compared cabozantinib vs. everolimus in the patients with advanced RCC that had disease progression after prior antiangiogenics. All

the patients were allocated into two arms: cabozantinib at a dose of 60 mg daily and everolimus at 10 mg daily. Median PFS and ORR were superior in the experimental arm: 7.4 vs. 3.8 months (HR 0.58; 95% CI 0.45–0.75), and ORR 21 vs. 5%, respectively. A planned interim analysis showed that OS was improved in the cabozantinib arm (HR 0.67; 95% CI 0.51–0.89; P = 0.005). Grade 3–4 AEs were reported in 74% of cabozantinib arm and 65% of the everolimus arm.

In April and July 2016, the FDA and the EMA approved cabozantinib for the treatment of patients with an advanced RCC refractory to antiangiogenics, respectively.

The most recent CABOSUN phase II multicenter trial evaluated cabozantinib in a population of patients with intermediate or poor prognosis mRCC. Patients are randomized 1:1 to cabozantinib of 60 mg daily or sunitinib 50 mg daily. The primary endpoint was PFS. Cabozantinib associated with a better median PFS than sunitinib in the first line setting (8.2 vs. 5.6 months; HR, 0.66; 95% CI, 0.46–0.95; one-sided p = 0.012). ORR was 46% for cabozantinib vs. 18% for sunitinib. Grade 3–4 AEs of all causality were 67% for cabozantinib and 68% for sunitinib that comprised fatigue, hypertension, diarrhea palmar-plantar erythrodysesthesia, and hematological toxicity. Sixty-seven percentage of the patient allocated to cabozantinib caused grade 3 or 4 AEs, which included hypertension (28%), diarrhea (10%), and fatigue (6%) [3].

Based on the data of CABOSUN trial, cabozantinib has been listed in the first-line setting for poor- and intermediate- risk of mRCC patients in the updated version 2018 NCCN guideline.

2.1.7. Bevacizumab along with interferon

Bevacizumab is an endovenous recombinant human monoclonal antibody that binds and neutralizes VEGF-A, which are biologically active. It was also the first antiangiogenic treatment to show clinical efficacy in advanced RCC.

In a randomized double-blind phase II trial, 116 patients with mRCC with measurable metastatic disease were randomized into three arms: placebo, low-dose (3 mg/kg), or high-dose of bevacizumab (10 mg/kg) every 2 weeks. The results demonstrated a significant prolongation of PFS in the high-dose bevacizumab comparing to the placebo group (HR 2.55; P < 0.001) [27]. A multicenter phase III trial (AVOREN) compared bevacizumab in combination with IFN-α to IFN-α in the first line of treatment. Six hundred and forty nine patients were enrolled. The median PFS was significantly longer in the arm with combination arm than in the arm with the monotherapy (10.2 vs. 5.4 months), and ORR (30.6 vs. 12.4%) was significantly different. A trend toward improved OS was observed although not statistical significantly (23.3 vs. 21.3 months). These results could be due to the crossover to the bevacizumab plus IFN-α group before progression. The main side effects related to the combination included asthenia (11%), fatigue (13%), proteinuria (8%), and hypertension (6%) [28].

The CALGB90206, which is a prospective, randomized, phase III trial clinical carried out in United States showed the similar results with the AVOREN trial, with 732 treat-naïve patients randomized 1:1 to monotherapy of IFN-α or bevacizumab plus IFN-α. The combination group produced better PFS (8.5 vs. 5.2 months) and ORR (25.5 vs. 13.1%). Also, no significant differences exist in OS between the two groups [29].

Bevacizumab plus IFN was registered in November 2007 and in August 2009 by the EMA and the FDA, respectively, for untreated patients with mRCC of good or intermediate risk (Memorial Sloan Kettering Cancer Center (MSKCC) classification.

2.2. Targeting the mammalian target of rapamycin (mTOR) pathway

TORC1 and TORC2 are two multiprotein complexes, which include a serine threonine kinase called mTOR, and they can regulate micronutrients, cell growth, apoptosis, and angiogenesis. mTOR inhibitor can inhibit small-molecule kinase, which lies downstream in the phosphatidylinositol 3-kinase (PI3K)-AKT pathway.

2.2.1. Temsirolimus

Temsirolimus is an intravenous mTOR inhibitor, which inhibits the TORC1 complex by binding FKBP12 protein. Temsirolimus showed promising effectiveness in patients with mRCC in the early phase clinical trials [30, 31].

A phase III, multicenter open-label, clinical trial in untreated mRCC patients were carried out with three of six unfavorable prognosis factors. Six hundred and twenty six patients were randomized equally to three arms of treatment: IFN, temsirolimus, or IFN plus temsirolimus. The primary endpoint was OS. Patents were stratified with prior nephrectomy and geographic region. Patients who received temsirolimus alone experienced the best clinical outcome, showed a significant improvement in OS for 10.9 months (p = 0.008 vs. IFN 7.3 months) while the toxicity profile was acceptable. The combination group failed to improve the OS and PFS and also with increased adverse reactions [32]. About 20% of the patients included in this trial with nonclear cell RCC also benefited from temsirolimus.

Based on these data, in 2007, this drug was approved by both the FDA and the EMA as a category 1 recommendation for first-line treatment of poor-risk patients with relapsed or medically unresectable predominantly clear cell stage IV renal carcinoma.

2.2.2. Everolimus

Everolimus is an orally administered inhibitor of mTOR, and it showed promising antitumor activity in patients with advanced RCC previously treated with cytokines [33]. Based on the results, a phase III, randomized, double-blind trial was designed (RECORD1) to evaluate the efficacy and toxicity of everolimus vs. placebo for the treatment of mRCC patients whose disease had progressed on the treatment of VEGFR inhibitors (sorafenib or sunitinib) [34]. The primary endpoint was PFS, and the secondary endpoints included OS and safety. The results of the second interim analysis indicated that the everolimus arm was associated with better PFS than the placebo arm (4.9 vs. 1.9 months; HR 0.33; p < 0.001). However, no significant differences exist in median OS between both arms (14.8 vs. 14.4 months; HR 0.87; p = 0.162). The most commonly AEs observed in the everolimus treatment arm were stomatitis (40%), rash (25%), and fatigue (20%), which were mostly mild or moderate in severity. Pneumonitis was caused in 8% of the patients with everolimus treated, eight of them reaching a grade 3 of severity.

A recent randomize phase III trial compares nivolumab with everolimus in patients with advanced mRCC who were previously treated, indicated that the OS was longer occurred with nivolumab than with everolimus (25.0 vs. 19.6 months, p = 0.002) [35]. In METEOR trial, which is also a phase III trial, randomized 658 patients to receive cabozantinib or everolimus; the result showed longer PFS with cabozantinib compared to everolimus (7.4 vs. 3.8 months; HR:0.58; p < 0.001) [36].

Based on the above data, in 2009, everolimus was approved by both the FDA and the EMA as a category 2A subsequent therapy option for the treatment of mRCC after antiangiogenics.

2.3. Immunotherapy

T cells play an important role in anti-tumor activity through stimulatory and inhibitory system. Due to high mutation and other factors, immune system has been made to be self-tolerant by cancer cells, the most active immunotherapy recently be studied include: anti-PD1, anti-PDL1, and anti-CTLA-4. Immunotherapy with monoclonal antibodies against the programmed cell death 1 (PD-1) protein has become an important and effective therapy of advanced melanoma and nonsmall cell lung cancer and also is now being tested in a large number of malignancies. It has been tested in RCC with success results.

2.3.1. Nivolumab

Nivolumab is a fully human IgG4 antibody against PD-1. A phase I clinical trial was designed to determine the safety and tolerability of nivolumab with treatment-refractory solid tumor, one RCC patient previously treated experienced an overall PR that lasted more than 16 months after only three infusions of nivolumab [37]. These findings prompted the clinical development of this compound in the treatment of mRCC.

A randomized open-label phase III study CheckMate 025 compared nivolumab with everolimus in patients with previously treated mRCC. Eight hundred and twenty one patients were randomly assigned 1:1 to receive nivolumab or everolimus. The primary end point was OS. Patients in the experimental arm experienced better median OS of 25 vs. 19 months (HR 0.73; p = 0.002) and greater ORR (25 vs. 5%; p<0.001). Grade 3–4 toxicities occurred in 19 and 37% for patients receiving nivolumab and everolimus, respectively [35].

Based on the results of the CheckMate 025, nivolumab was approved by the FDA and the EMA as a category 1, preferred subsequent therapy option in November 2015 and February 2016, respectively for the treatment of RCC after progression to TKI therapy.

The clinical development of nivolumab in RCC is currently very intense, and multiple studies are testing the value of strategies in several ways. Phase I CheckMate 016 clinical trial evaluated the efficacy and safety of the combination of nivolumab with the anti-CTLA4 ipilimumab [38]. CheckMate 214 (NCT02231749) evaluates the role of ipilimumab in combination with nivolumab in patients who do not response after monotherapy of nivolumab, and results are highly awaited.

2.4. Target therapy for nonclear cell RCC

The only available category 1 preferred recommendation for systemic treatment of nonclear cell RCC (nccRCC) is temsirolimus, and it was commended in patients with poor-risk features [32]. Although other targeted agents against the VEGF and mTOR pathways are frequently used in the treatment of nccRCC, optimal first-line agent is much less defined and the outcomes are inferior to that in patients with ccRCC [39, 40]. Immune checkpoint inhibitors appear promising effect in early clinical trials and we look forward to a good result in the updating clinical trial.

3. Upcoming therapies in RCC

3.1. Last generation for targeting VEGF/VEGFR

3.1.1. Dovitinib

Dovitinib (TKI-258) is an oral tyrosine-kinase inhibitor that inhibits VEGF and FGF receptors. In a multicenter phase III study, patients who previously received VEGF-targeted therapy or mTOR inhibitor were randomized to dovitinib or sorafenib. The results indicated that the mPFS was 3.7 months in dovitinib group vs. 3.6 months in sorafenib group, showing improvement in mPFS, however, with no significant difference [41]. A phase II clinical trial has been designed to find out the usefulness of dovitinib in the initial treatment for patients with advanced kidney cancer, and the study will additionally look for changes in the genetic makeup of tumor cells.

3.1.2. Trebananib

Angiopoietin-2 (Ang2) exhibits broad expression in the remodeling vasculature of tumors but not in the normal tissues. Trebananib (AMG-386) can bind to angiopoietin 1 and 2 and block their union with the Tie2 receptor tyrosine kinase, showing its antiangiogenic effect. In preclinical and clinical phase I studies, AMG-386 showed a good safety profile in inhibiting tumor growth [42]. A randomized phase II trial showed that AMG-386 plus sorafenib reach a RR of 38% in RCC patients previously treated [43].

3.2. Immunotherapy

3.2.1. Pembrolizumab

Pembrolizumab (MK-3475) is a highly selective IgG4-humanized monoclonal antibody, which prevents the binding of PD-1 with PD-L1 and PD-L2. A phase I study evaluated the safety, tolerated does, and antitumor effect of pembrolizumab in patients with advanced solid tumors. It showed durable antitumor activity in multiple solid tumors including RCC [44]. There are two clinical trials NCT02212730 and NCT02853344, both of which are currently

recruiting, are going to test the effect of pembrolizumab in the neoadjuvant treatment for localized RCC and in untreated mRCC, respectively as monotherapy.

3.2.2. Avelumab

Avelumab (MSB0010718C) is a human IgG1 monoclonal antibody against PD-L1. Avelumab binds to PD-L1 inhibiting its binding to PD-1 and therefore inhibiting its activation of T cells and restoring anticancer immune function. In an open-label, single-center, phase 1a trial, safety and activity of this compound was tested in multiple solid tumors including RCC and prompted the further research for this drug [45]. An open, randomized phase II trial SUAVE, which is recruiting is going to compare avelumab followed by sunitinib with the opposite sequence. The effect of avelumab in the combination therapy is also being evaluated. A phase III, multinational, randomized trial is going to compare avelumab with axitinib vs. sunitinib in advance renal cell cancer which is currently recruiting (NCT02684006).

3.2.3. Atezolizumab

Atezolizumab (MPDL-3280A) is a PD-L1-specific monoclonal antibody, which inhibits the binding of PD-L1 to PD-1. Based on the promising date in the phase I clinical trial [46], a further phase II clinical trial IMmotion 150 enrolled untreated mRCC patients, and random-ized them into three arms, atezolizumab alone, atezolizumab with bevacizumab, and sunitinib alone. Preliminary result showed no significant difference in PFS between the two arms with immunotherapy, PD-1+ patients showed a trend of survival benefit, although with no signifi-cant difference. The IMmotion 151 phase III trial is ongoing to assess the combination of atezolizumab with sunitinib in mRCC.

3.2.4. Ipilimumab

Ipilimumab is an antibody against CTLA-4 and it shows powerful antitumor activity and clinical experience in the treatment of patients with metastatic melanoma. Therefore, a phase II trial was conducted in patients with mRCC, observing a 10% partial RR, 33% of the patients experienced a grade III or IV immune-mediated toxicity [47]. The efficacy of ipilimumab combine with other drugs is also being evaluated in some trials, like the phase III, randomized study CheckMate 214, comparing the combination of nivolumab and ipilimumab with sunitinib monotherapy in previously untreated local advanced RCC or mRCC. Ipilimumab is also being investigated in association with other drugs for the treatment of advanced RCC, like Check-Mate 214 study or Keynote-29 study.

Due to the remarkable development of the advanced in the molecular mechanism and cytoge-netic of tumor in the last decade, targeted agents directed against VEGF, VEGFR, and mTOR have been important therapy in mRCC. Immune checkpoint inhibitors also appear promising power, and a lot of novel targets including small molecule TKIs and immunotherapies are entering clinical trials, which will update the treatment paradigms in the future time. It is hoped that with better understanding of the molecular diversity of RCC, more effective and personalized therapeutic strategies can be developed against mRCC to make the patients obtain the maximum benefit.

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