Clear-cell renal cell carcinoma - A comprehensive review of agents used in the contemporary management of advanced/metastatic disease

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Abstract

Renal cell carcinoma represents the most common malignancy of the kidney and the majority of cases are categorized as clear cell carcinomas. The elucidation of the specific alterations in key molecular and metabolic pathways responsible for cancer development and progression have prompted the rationalization of our classification of this disease and have provided specific targetable molecules implicated in carcinogenesis. Although immunotherapy has been an established option in the treatment of metastatic renal cell cancer for many years, its role has been renewed and upgraded with the implementation of anti-angiogenic agents and immune checkpoint inhibitors in our treatment armamentarium. The future holds promise, as newer agents become available and combination regimens of immunotherapy with anti-angiogenic agents have become the standard of care in the management of metastatic disease and are currently being evaluated in earlier settings. Proper patient selection and individualization of our treatment strategies are of utmost importance in order to provide optimal care to patients suffering from renal cell carcinoma.

Introduction

Clear-cell renal cell carcinoma (ccRCC) represents the most common malignancy of the kidney, accounting for 80% of renal carcinomas.[1] It is estimated that new renal cancer cases in the United States comprise approximately 5% of all new diagnoses of malignancy, establishing kidney cancer as the 6th most common cancer in men and the 9th most common cancer in women, with a median age at diagnosis of 64 years. It is projected that 73,750 new diagnoses of RCC will be made and 14,830 people will lose their lives from this disease during 2020.[2]

Current epidemiological trends reflect the wide implementation of various diagnostic and screening techniques for unrelated reasons, that result to a migration towards earlier stages at diagnosis.[3] Furthermore, the stabilization and/or decline of RCC incidence, observed mainly in developed countries, may be partially attributed to changes in the way of life, and especially in the decline of smoking rates and the adoption of a generally healthier lifestyle.[4] Lastly, it can be expected that mortality rates may drop even further in the future, as novel therapies for advanced disease have provided significant results in clinical trials and have already been successfully implemented in clinical practice.

Partial or total nephrectomy cures the majority of patients with ccRCC. Nevertheless, locally advanced or metastatic (a/m) ccRCC is not amenable to surgery alone and accounts for about 20% of newly diagnosed cases, while about 30% of non-metastatic disease will develop metastases after surgery. Until 2005, long-term survival was possible in only 5% of patients. The advances in our knowledge regarding the biological characteristics determining the behavior of RCC and especially on angiogenesis and anti-tumor immune response, led to rapid developments in systemic therapy of a/m ccRCC in the last 15 years, which have resulted in significant prolongation of survival of patients suffering from this disease. The current review focuses on the agents, which have been associated with this remarkable progress in the management of a/m ccRCC (Tables 1 and 2).

Systemic therapy of metastatic renal cell carcinoma

Single agent therapy - Agents targeting VEGF/VEGFRs-driven angiogenesis in renal cell carcinoma

Sorafenib

Sorafenib is a multitargeted TKI with antiangiogenic and antiproliferative properties.[5] It was one of the first targeted therapies to be approved for the treatment of advanced RCC, following the results of the phase III TARGET trial, that provided a PFS benefit of 5.5 months over placebo in cytokine-pretreated patients.[6]

In the following years Sorafenib has been employed as a comparator for newer drugs in phase III trials in the first-, second- and third line of therapy. Most of these trials showed superiority for the investigational arm, thus displacing Sorafenib as the preferred treatment option for mRCC. However, real-world data suggest that Sorafenib is still a valid option for heavily pre-treated patients with advanced RCC who are still candidates for systemic therapy.[7]

Table 1. Summary of pivotal phase III trials for the treatment of metastatic renal cell carcinoma.

Trial	Treatment arms	Setting	Previous treatment	N	ORR (%)	PFS (months)	OS (months)
CheckMate 9ER	Pembrolizumab+Cabozantinib *vs* Sunitinib	1st line	N/A	651	55.7 *vs* 27.1 (P<0.0001)	16.6 *vs* 8.3 HR: 0.51 95% CI: 0.41-0.60 (P<0.001)	NR *vs* NR HR: 0.60 98.89% CI: 0.40-0.89 (P=0.0010)
Keynote 426	Pembrolizumab+Axitinib *vs* Sunitinib	1st line	N/A	861	59.3 *vs* 35.7 (P<0.001)	15.1 *vs* 11.1 HR: 0.69 95% CI: 0.57-0.84 (P<0.001)	NR *vs* NR HR: 0.53 95% CI: 0.38-0.74 (P<0.0001
JAVELIN Renal 101	Avelumab+Axitinib *vs* Sunitinib	1st line	N/A	886	ITT 51.4 *vs* 25.7 PD-L1(+) 55.2 *vs* 25.5	ITT 13.3 *vs* 8.0 HR: 0.69 95% CI: 0.574-0.825 (P < 0.0001) PD-L1 (+) 13.8 *vs* 7.0 HR: 0.62 95% CI: 0.490-0.777 (P < 0.0001)	PD-L1(+) 13.8 *vs* 8.4 HR=0.69 95% CI: 0.56-0.84 (P<0.001)
IMmotion 151	Atezolizumab+Bevacizumab *vs* Sunitinib	1st line	N/A	915	ITT: 37 *vs* 33 PD-L1(+): 43 *vs* 35	PD-L1(+) 11.2 *vs* 7.7 HR=0.74 95% CI: 0.57-0.96 (P=0.0217)	ITT: 43% *vs* 42% 95% CI: 0.76-1.14 (HR= 0.93;95% CI:0.76–1.14; (p=0.4751) PD-L1(+): 42% *vs* 45% (HR=0.84; 95% CI:0.62–1.15; P=(0.2857)
TARGET	Sorafenib *vs* Placebo	2nd line	IL-2, IFN-a	903	NA	5.5 *vs* 2.8 HR=0.44 95% CI: 0.35-0.55 (P<0.000001)	17.8 *vs* 15.2 HR = 0.88 (P=0.146)
1034	Sunitinib *vs* IFN-a	1st line	N/A	750	31 *vs* 6 (P<0.001)	11 *vs* 5 HR: 0.42 95% CI:0.32-0.54 (P<0.001)	26.4 *vs* 21.8 HR = 0.818 95% CI 0.669-0.999 (P=0.049)
COMPARZ	Pazopanib *vs* Sunitinib	1st line	N/A	1110	31 *vs* 25 (P=0.03)	8.4 *vs* 9.5 HR: 1.047 95% CI: 0.90-1.22	28.3 *vs* 29.1 HR: 0.92 95% CI: 0.79-1.06
AXIS	Axitinib *vs* Sorafenib	2nd line	Sunitinib, Bevacizumab+ IFNa, Temsirolimus, Il-2	723	19 *vs* 9 (P=0.0001)	6.7 *vs* 4.7 HR: 0.665 95% CI: 0.544-0.812 (P<0.0001)	20.1 *vs* 19.2 HR: 0.969 95% CI: 0.800-1.174 (P=0.3744)
METEOR	Cabozantinib *vs* Everolimus	2nd line	Sunitinib, Pazopanib, Axitinib, Sorafenib, Bevacizumab, IL-2, IFN-a, Nivolumab	658	17 *vs* 3 (P<0.0001)	7.4 *vs* 3.8 HR: 0.58 95% CI, 0.45-0.75 (P<0.001)	21.4 *vs* 16.5 HR 0.67 95% CI 0.53-0.83 (P=0.0003)
ARCC	Temsirolimus *vs* Temsirolimus/ IFN-a *vs* IFN-a	1st line	N/A	626	9.1 *vs* 9.5 *vs* 5.3 (P=0.162)	3.7 *vs* 3.8 *vs* 1.9 HR:0.76 95% CI: 0.62-0.94 (P=0.0107)	8.4 *vs* 10.9 *vs* 7.3 HR: 0.93 95% CI: 0.75-1.15 (P=0.492)
INTORSECT	Temsirolimus *vs* Sorafenib	2nd line	Sunitinib	512	8 *vs* 8	4.3 *vs* 3.9 HR: 0.87 95% CI: 0.71-1.07 (P=0.19)	12.3 *vs* 16.6 HR = 1.31 95 % CI: 1.05-1.63 (P=0.01)
RECORD 1	Everolimus *vs* placebo	2nd line	Sunitinib, Sorafenib	416	1.8 *vs* 0.0	4.9 *vs* 1.9 HR= 0.33 (P<.001)	14.8 *vs* 14.4 HR: 0.87 (P=0.162)
Checkmate 25	Nivolumab *vs* Everolimus	2nd/3rd line	Sunitinib, Pazopanib, Axitinib	821	25 *vs* 5 (P<0.001)	4.6 *vs* 4.4 HR: 0.88 95% CI, 0.75-1.03 (P=0.11)	25 *vs* 19.6 HR: 0.73 98.5% CI: 0.57- 0.93 (P=0.002)
Checkmate 214	Nivolumab+ Ipilimumab *vs* Sunitinib	1st line	N/A	1096	42 *vs* 27 (P<0.001)	11.6 *vs* 8.4 HR: 0.82 99.1% CI, 0.64-1.05 (P=0.03)	NR *vs* 26.0 (HR: 0.63, P<0.001)

N/A, not applicable; NR, not reached; ITT, intention to treat; CI, confidence intervals; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; ORR, objective response rate.

Sunitinib

Sunitinib has long been the standard 1st-line therapy for mRCC. It is an oral multiple TKI including those of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-a, PDGFR-b.[8] Its first approval by the Food and Drug Administration (FDA) followed the unprecedented tumor activity shown in two phase II trials in cytokine-refractory mRCC with objective response rates (ORRs) approximating 40%.[9,10] A pivotal phase III trial confirmed its superiority over IFN-a, doubling PFS in treatment-naïve patients with mRCC.[11] Multiple subsequent real-word studies confirmed both the efficacy and tolerability of this agent. Thus, Sunitinib introduced a new era with 2-fold increase in OS compared to historical controls treated with cytokines.[12] The introduction of ICIs has changed the treatment paradigm in 1st-line in mRCC. Currently, Sunitinib is recommended as an alternative first-line therapy for patients who cannot receive the Pembrolizumab-Axitinib or the Nivolumab-Ipilimumab combinations.[13] It should be underlined, that subgroup analyses from the KEYNOTE 426 study comparing Pembrolizumab/Axitinib *vs.* Sunitinib has not confirmed the superiority of the combination among IMDC favorable-risk patients.[14] Therefore, the role of TKI monotherapy in this subgroup has not been defined yet.

Pazopanib

Pazopanib is an oral small-molecule multi-kinase inhibitor that primarily inhibits VEGFR-1, VEGFR-2 and VEGFR-3, PDGFR-α and PDGFR-β, and the stem-cell factor receptor c-kit.[15] Its activity in RCC was evaluated in a phase II clinical trial in localized recurrent or metastatic ccRCC, in patients who were either treatment-naive or were treated with one regimen of cytokine or a Bevacizumab-containing regimen, producing encouraging ORR and PFS results.[16] Further insight on its activity was provided by a second phase II trial, in patients with mRCC who had developed resistance to Sunitinib or Bevacizumab.[17] In a phase III trial, in a group of patients consisting of both treatment-naive cases and cases previously treated with cytokine therapy, Pazopanib was compared to placebo in a 2:1 randomization. The study met its primary endpoint providing a median PFS of 9.2 months over 4.2 months favoring Pazopanib, also showing a numerical but not statistically significant difference in OS, attributed in the early and extensive crossover from the placebo to the Pazopanib group.[18] Two more clinical trials were carried out, directly comparing it with the standard of care Sunitinib. In the COMPARZ study, Pazopanib proved to be non-inferior to Sunitinib in terms of PFS, OS in treatment-naive patients.[19] The two drugs were also compared in the PISCES trial, which compared treatment preferences, after having received alternating treatment cycles of Sunitinib and Pazopanib. 70% of the patients preferred Pazopanib, 22% selected Sunitinib, while 8% claimed no preference. These results have been attributed to a relatively better quality of life (QoL) and less fatigue resulting from Pazopanib treatment.[20]

Based on the above results, the position of Pazopanib in the landscape of the treatment of mRCC has been similar to that of Sunitinib.

Axitinib

Axitinib is an oral third-generation TKI and a potent VEGFR inhibitor with a 10-fold higher affinity than other TKIs.[21] Axitinib is well tolerated, demonstrating a manageable toxicity profile consistent with expected adverse events of VEGFR-TKIs.

The AXIS phase III trial showed that Axitinib was superior to Sorafenib in 2nd-line but failed to prove its superiority in 1st-line.[22,23] Therefore, Axitinib monotherapy is currently approved by both FDA and European Medicines Agency (EMA) in 2012 for the treatment of advanced RCC, after failure of one prior systemic therapy.

Cabozantinib

Cabozantinib is a small multiple TKI, including *MET*, *VEGFRs* and *AXL*. *MET* and *AXL* are commonly upregulated in RCC, as a result of *VHL* inactivation, while *MET* is also implicated in the development of resistance to VEGF-targeting therapies, as manifested in preclinical models.[24]

The activity of Cabozantinib in RCC was initially demonstrated in a single-arm study, where objective responses and disease control were noted in patients resistant to VEGFR and mTOR inhibitors.[25] In a randomized, open-label phase III trial that followed, Cabozantinib was compared to Everolimus in patients with ccRCC that have progressed after at least one line of therapy targeting the VEGFR. The trial demonstrated a significant PFS benefit of for Cabozantinib (7.4 *vs.* 3.8 months). In subsequent analysis, a significant prolongation of the secondary endpoint of OS was also shown met, with a median OS of (21.4 *vs.* 16.5 months).[26]

In the randomized phase II CABOSUN trial, Cabozantinib proved superior to Sunitinib as initial therapy in patients with locally advanced or metastatic RCC of intermediate or poor risk.[27] Based on these two trials, Cabozantinib has gained EMA and FDA approval for the treatment of mRCC in the first line in treatment-naïve individuals with intermediate or poor risk tumors, and in subsequent lines of therapy, following prior VEGF-targeted therapy.

Single agent therapy - Agents targeting the PI3K/Akt/mTOR pathway

Temsirolimus

Temsirolimus is a highly selective inhibitor of mTOR, inhibiting its kinase activity and blocking the cell cycle in G1 phase.[28] Its

Table 2. Current treatment options for metastatic clear-cell renal cell carcinoma.

Risk category	First line		Second line		Subsequent lines	
	Preferred	Alternative	Preferred	Alternative	Preferred	Alternative
Favorable	Pembrolizumab-Axitinib	Sunitinib Pazopanib	Nivolumab Cabozantinib	Lenvatinib-Everolimus Everolimus Axitinib Sunitinib Pazopanib	Axitinib Lenvatinib-Everolimus	Sunitinib Pazopanib Sorafenib
Intermediate and Poor	Pembrolizumab-Axitinib Nivolumab-Ipilimumab	Cabozantinib Sunitinib Pazopanib Temsirolimus	Nivolumab Cabozantinib	Lenvatinib-Everolimus Everolimus Axitinib Sunitinib Pazopanib	Axitinib Lenvatinib-Everolimus	Sunitinib Pazopanib Sorafenib

early clinical development revealed an excellent tolerability profile, as well as a clinical benefit demonstrated mostly in patients with intermediate or poor prognostic features.[29] Consequently, in its pivotal phase III ARCC trial, Temsirolimus was evaluated as first-line treatment in a population of previously untreated patients with adverse or intermediate prognostic characteristics, either alone or in combination with IFN-a, while both arms were also compared to IFN-a monotherapy. The results demonstrated a clear survival benefit for the Temsirolimus-containing regimens, with an OS of 7.3 months for IFN-α *vs* 8.4 months for the combination, and 10.9 months for Temsirolimus alone. A subgroup analysis suggested maximum benefit of Temsirolimus in patients of poor prognosis and of non-clear cell histology.[30] Based on these results, Temsirolimus was approved for the first-line treatment of patients with poor prognostic features. In a rapidly evolving treatment landscape, however, the use of Temsirolimus is extremely limited.

In second-line, Temsirolimus was compared to Sorafenib in the phase III INTORSECT trial, where a significant survival advantage was observed in the Sorafenib arm, with no differences between the two arms in the primary endpoint of PFS.[31]

Everolimus

Everolimus (RAD001) is another derivative of Rapamycin which was developed as an orally administered inhibitor of mTOR.[32] In the phase III RECORD 1 trial it provided a PFS benefit over placebo in patients pretreated with Sunitinib or Sorafenib, and it gained FDA and EMA approval for the second-line treatment of mRCC.[33] However, two major phase III trials proved the superiority of Nivolumab and Cabozantinib over Everolimus in this setting, thus limiting the utilization of this agent.[26,34]

Single agent therapy - Agents targeting PD-1/PD-L1 interaction

Nivolumab

Nivolumab is a fully human IgG4 PD-1 immune checkpoint inhibitor antibody that selectively blocks the interaction between PD-1, which is expressed on activated T cells, and its ligands PD-L1/L2, that are expressed on immune cells and tumor cells.[35] After a phase 2 trial in previously treated patients with mRCC demonstrated ORR of 20-22% and OS 18.2-25.5 months,[36] NIVO was compared to Everolimus in the phase III CheckMate 025 trial in patients with ccRCC who had received one or two prior lines of antiangiogenic therapies. Median OS was significantly prolonged by Nivolumab: 25.0 months for Nivolumab *vs* 19.6 months for Everolimus. The OS curves separated early, and the study also demonstrated a higher rate of objective responses in the NIVO arm, and many of them were durable. The benefit of Nivolumab was consistent, regardless of MSKCC prognostic score, number of prior antiangiogenic therapies, geographic region and PD-L1 expression.[34] As a result, Nivolumab monotherapy is recommended as a preferred agent for the treatment of ccRCC after anti-VEGF/VEGFR failure in the NCCN, ESMO and EAU guidelines.

Pembrolizumab

Pembrolizumab as a single agent has demonstrated convincing activity in untreated patients with a/mccRCC. In a phase II trial, which has been reported only in abstract form, Pembrolizumab achieved an objective response rate of 38% across all IMDC risk groups and even higher ORRs of 42% and 50% in patients in IMDC intermediate/poor-risk patients and patients with PD-L1-positive tumors, respectively.[37]

Combinations

Everolimus-lenvatinib

Lenvatinib is an oral multi-targeted TKI of VEGFR1-3, FGFR1-4, PDGFRβ, RET, and KIT. Although previous combination strategies of the mTOR inhibitors Everolimus and Temsirolimus with TKIs did not produce encouraging results, preclinical data in human RCC xenograft mouse models showed promising results with the combination Lenvatinib-Everolimus, thus prompting its clinical evaluation. In a phase II randomized trial in 2nd-line, the combination was superior in terms of OS, PFS and ORR over Everolimus, while Lenvatinib monotherapy failed to produce OS benefit.[38] Based on these results the combination gained FDA and EMA approval for the treatment of mRCC after prior TKI therapy.

Pembrolizumab-axitinib

The phase III KEYNOTE 426 (NCT02853331) evaluated the efficacy of the combination of Pembrolizumab and Axitinib *versus* Sunitinib monotherapy in treatment-naïve patients with advanced or metastatic RCC.[14] This trial followed the impressive results of a phase Ib study, producing a mPFS of 20.9 months, durable responses and acceptable safety profile.[39] At interim analysis, the KEYNOTE 426 met both its primary endpoints. After a median follow-up of 12.8 months, the estimated percentage of patients who were alive at 12 months was 89.9% in the Pembrolizumab-Axitinib group and 78.3% in the Sunitinib group and mPFS was 15.1 months in the combination group and 11.1 months in the Sunitinib group. PFS benefit was observed across all IMDC risk categories and was consistent, regardless of PD-L1 expression. These results led to the FDA and EMA approval of the Pembrolizumab-Axitinib regimen, and the combination is now recommended as a front-line therapeutic option by the ESMO, NCCN and EAU guidelines, irrespective of IMDC prognostic subgroups and PD-L1 biomarker status. Importantly, complete response (CR) rate exceeded 10% among favorable-risk patients, in an analysis following the main publication. More mature survival data and patient-reported outcomes are awaited.

Nivolumab/ipilimumab

Ipilimumab, a fully human anti-CTLA-4 mAb, currently approved for the treatment of metastatic melanoma, was initially tested in a small clinical trial of a mixed population of mRCC patients, consisting of both treatment-naïve and previously treated with IL-2 individuals. In this early trial, it demonstrated responses ranging between 5 and 12.5% among different cohorts, corresponding to different dosing schedules, at the price of excessive toxicity. The high rate of toxicities precluded its further development as monotherapy for this disease.[40] However, acceptable toxicity profile was observed using a combination Nivolumab/Ipilimumab, where Ipilimumab was used only in the first 4 cycles of therapy.[41] This combination was evaluated in the randomized, open-label, phase III Checkmate 214 trial, *versus* Sunitinib, in treatment-naïve patients with advanced or metastatic RCC. The trial met its primary endpoints, with the combination producing superior 12- and 18-month survival rates, ORR and mOS in patients with intermediate and poor IMDC risk. CR rate also exceeded 10% with this combination. Importantly, Sunitinib achieved better outcomes in an exploratory analysis of favorable-risk patients.[42]

Based on the above-mentioned trial, Nivolumab/Ipilimumab combination has gained approval in USA and Europe, for the treatment of intermediate or poor risk, previously untreated, advanced or metastatic RCC.

Avelumab/axitinib

Avelumab is an IgG1 mAb targeting PD-L1.[43] Its combination with Axitinib has been initially evaluated in the JAVELIN Renal 100 study.[44] The preliminary results of this trial indicated that the combination is characterized by an encouraging antitumor activity and by a manageable safety profile, thus prompting the launch of the phase III JAVELIN Renal 101 trial of the combination against Sunitinib in treatment-naïve mRCC patients.[45] The trial succeeded in producing a statistically significant PFS benefit both in PD-L1(+) patients and in the overall population. Among the 560 patients with PD-L1-positive tumors (63.2%), the mPFS was 13.8 months with Avelumab plus Axitinib, as compared to 7.2 months with Sunitinib. In the overall population, the mPFS was 13.8 months, as compared to 8.4 months with Sunitinib.

Atezolizumab/Bevacizumab

Atezolizumab is a humanized anti-PD-L1 IgG1 mAb.[46] The randomized phase II IMmotion 150 trial evaluated Atezolizumab in treatment-naïve patients with mRCC, both as monotherapy and in combination with Bevacizumab, *versus* Sunitinib.[47] Both the combination and Atezolizumab monotherapy provided encouraging results, thus prompting the further evaluation of the combination over Sunitinib in the phase III trial IMmotion 151. This trial succeeded in its co-primary endpoint of improved PFS in PD-L1-positive patients, with a mPFS of 11.2 months with the combination *versus* 7.7 months with Sunitinib (P=0.02).[48] Nevertheless, due to the lack of favorable OS results, it is doubtful if further development of this combination will be pursued.

Nivolumab/Cabozantinib

The results of a randomized, phase III trial comparing the combination of Nivolumab/Cabozantinib *versus* Sunitinib were reported in the recent ESMO20 Congress.[49] The combination was superior to Sunitinib for PFS, OS, and response rate. There was a consistent benefit of the combination over Sunitinib in numerous subgroups including age, sex, PD-L1 expression, bone metastases, IMDC risk group, and region of the world. It is, therefore, expected that this combination will also gain FDA and EMA approval for 1st-line treatment of a/m ccRCC.

Optimizing the sequence of novel agents in the treatment of metastatic renal cell carcinoma

First line

Several factors should be taken into consideration in the choice of 1st-line therapy in a/mRCC. Modern immunotherapy is still unavailable in many countries, while these agents should be used with caution in patients with history of autoimmune disease. Patients preferences should always be discussed. For favorable-risk patients, active surveillance of slow growing asymptomatic disease or local definitive therapy for oligometastatic disease without systemic therapy are still valid options.

Immunotherapy combinations now represent the standard systemic therapy for treatment-naïve patients. OS analyses of all reported randomized trials suggest that a sizable proportion of patients enjoy long-term, progression-free survival. Longer follow up is necessary to determine if these outcomes indicate cure for the majority of these patients. The Pembrolizumab-Axitinib combination is indicated for all patients, irrespective of risk category or PD-L1 expression. Nivolumab-Ipilimumab, on the other hand, is a valid first-line option only for intermediate or poor-risk patients. When immunotherapy is contraindicated or unavailable, Sunitinib and Pazopanib may be used, while Cabozantinib is also indicated in intermediate/poor risk patients. The choice will become more complicated after the expected approval of Nivolumab-Cabozantinib. On the other hand, the role of TKI monotherapy in favorable risk patients may be more clearly defined when mature OS data for this subgroup becomes available. At the moment, the higher CR rate reported for the combination Pembrolizumab-Axitinib compared to Sunitinib monotherapy renders the former the preferred therapy.

Second line

Following the results of CheckMate 025 and METEOR, Nivolumab and Cabozantinib represent the best options for TKI-only pre-treated patients. Choosing between the two cannot be based on solid data, but bone metastases may have a more favorable outcome with Cabozantinib. Other options include Axitinib and the combination Lenvatinib-Everolimus.

The development of the new treatment paradigm in first-line has created new challenges in selecting the optimal therapy in 2nd-line following previous exposure to TKI/ICI or ICI/ICI combination. Sunitinib, Pazopanib and Cabozantinib have all been used in this setting with encouraging efficacy, although evidence is still of low level.[50]

Future perspectives

There has been unprecedented progress in the treatment of a/m RCC during the last 15 years, resulting in considerable improvement in prognosis. The two major classes of agents used in the current treatment paradigm are VEGFR TKIs and ICIs. Future research will focus in using these agents in a more personalized fashion, based not only of clinical characteristics but also in molecular profiling. At the same time current studies may further refine the role of combinations and monotherapies, especially in 1st-line. In the context of personalized treatment of a/mRCC, clinical research is currently studying new targeted therapies, developing approaches of individualizing current combination therapy and identifying promising biomarkers as tools for appropriate patient selection.

The long known critical importance of the VHL-HIF pathway, which controls the cellular response to hypoxia, in oncogenesis but also the clinical behavior of ccRCC, has focused interest on the development of novel agents targeting this pathway. A promising small molecule inhibitor of HIF-2 is currently under clinical evaluation and encouraging results have been already reported in small series of patients.[51]

The HCRN GU16-260 study was reported in ASCO 2020. Patients with a/mRCC received 1st-line nivolumab monotherapy. Ipilimumab salvage was added to those who did not achieve a partial remission by week 48 or those who experienced progressive disease at first tumor assessment (week 12).[52] The results presented suggest the feasibility and safety of this approach and a phase III study (BMS CM 209-8Y8) will formally address this issue directly in intermediate and poor-risk patients.[53]

Regarding patient selection for current standard therapies, the IMDC risk stratification represents the most valid tool in this respect, as already discussed. Nevertheless, intense research on identifying molecular characteristics, which could lead to more personalized approaches is ongoing. Markers, which have shown consistent predictive value in other cancers treated with ICI, such as PD-L1 expression in tumor cells and in immune cells and tumor mutational burden have failed to produce similar results in a/mRCC.[54,55] Instead, more complex molecular signatures may be of value. The role of NGS in RCC is evolving to consider the mutational landscape of metastatic RCC, ideally to identify predictive

markers that inform first-line treatment choice or direct patients to a targeted therapy. ccRCC exhibits enhanced vascular development and immune gene signatures relative to other histological subtypes, consistent with the unique role of the VHL-HIF pathway in their development and their relative sensitivity to immunotherapy. In the phase II IMmotion150, the validity of such a signature was investigated, by combining T-effector presence and function, IFN-γ response, angiogenic factors and myeloid inflammation genes. The improved response associated with the combination regimen *versus* ICI monotherapy in the immune-suppressed T$_{eff}$ ^{High}Myeloid^{High} subgroup may suggest that the addition of an antiangiogenic drug to ICI overcomes innate inflammation-mediated resistance.[47] Similar information was obtained in JAVELIN Renal 101. An immune-gene signature (different from that used in IMmotion150) was correlated with improved response to the combination arm, while increased angiogenesis was correlated with improved PFS in the Sunitinib arm.

Conclusions

The continuing expansion of our knowledge in molecular biology, cancer genetics and in the interactions between tumors and the immune system, is rapidly transforming our understanding of cancer, changing our approach to the diagnosis and treatment of this disease. This progress is particularly relevant in advanced/metastatic ccRCC, where the combination of ICIs with targeted agents have become standard practice and cure of sizable proportions of patients have been suggested by many recent clinical trials. The greatest challenge clinicians are likely to face in the near future is the use of these agents and combinations in a personalized approach, which will ensure optimum efficacy/toxicity balance and maximum cost effectiveness.

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