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Medical Oncology (2018) 35:156
https://doi.org/10.1007/s12032-018-1217-1

REVIEW ARTICLE

Contemporary treatment of metastatic renal cell carcinoma

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Received: 5 October 2018 / Accepted: 24 October 2018
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Abstract
Renal cell carcinoma is the 14th most common cancer worldwide. It is a heterogeneous group of histopathological entities, of which the most common is clear cell renal cell carcinoma. Approximately 20–30% of patients present initially with metastatic disease and an additional 20% will progress after radical surgical treatment. Metastatic disease that is non-feasible for surgical treatment remains incurable. Numerous studies have demonstrated that—with the introduction of new drugs—the treatment outcomes of metastatic disease have improved. The development of new therapies as well as the optimization and individualization of procedures allow us to hope for further progress in this area.

Keywords Renal cell carcinoma · Targeted therapy · Immunotherapy

Introduction

Renal cell carcinoma (RCC) is a heterogeneous group of histopathological entities, of which the most common is clear cell RCC, constituting 70–75% of all renal tumors. The remaining 10% and 5% constitute papillary and chromophobe RCCs, respectively. Between four and six percent of tumors cannot be assigned to any specific RCC subtypes [1].

RCC is the 14th most common cancer [2, 3]. Worldwide, in 2008, there were nearly 274,000 new cases of RCC and 72,000 kidney cancer-related deaths, with an age-standardized mortality rate of 2.2 per 100,000. The incidence rates are highest in Europe, North America, and Australia and lowest in India, Japan, Africa, and China. Globally, the standardized prevalence rate of RCC is 4 per 100,000 people per year [4].

RCC incidence has increased in the last two decades; however, in the recent years, this trend has been stopped and partially reversed. Due to increased availability of ultrasound and computed tomography, the number of the advanced renal tumors has decreased in favor of smaller, less advanced tumors. This translates into a better prognosis and lower mortality [5].

The most important factor in the RCC cancerogenesis is a mutation of the suppressor gene, von Hippel–Lindau (VHL), which is located on chromosome 3. Fusion of the VHL gene product (pVHL) with hypoxia-inducible factors (HIFs) leads to proteasome-mediated degradation. As a result of VHL mutation, such fusion is impossible. Inhibited HIF degradation leads to its pathological accumulation [6]. HIFs contribute to the transcription of growth factor coding genes: vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor alfa (TGF alfa). VEGF receptor activation triggers vascular proliferation (angiogenesis), which is essential for tumor growth. Von Hippel–Lindau syndrome is the most important inherited mutation associated with clear cell RCC, with an incidence of 1 in 36,000 births. VHL mutation is characterized by incomplete penetrance: only 40–50% of patient will develop ccRCC [7]. Furthermore, 80% of sporadic ccRCC are associated with inactivation or damage to the suppressor gene VHL and its product, the VHL protein [8] (Fig. 1).

Activation of protooncogene c-met on chromosome 7 results in the formation of the permanently activated receptor of the hepatocyte growth factor, which is linked with a hereditary form of papillary RCC (pRCC). This mutation is associated with pRCC type 1 [9]. Additionally, damage to the fumarate hydratase gene on chromosome 1 is involved in

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Published online: 27 October 2018

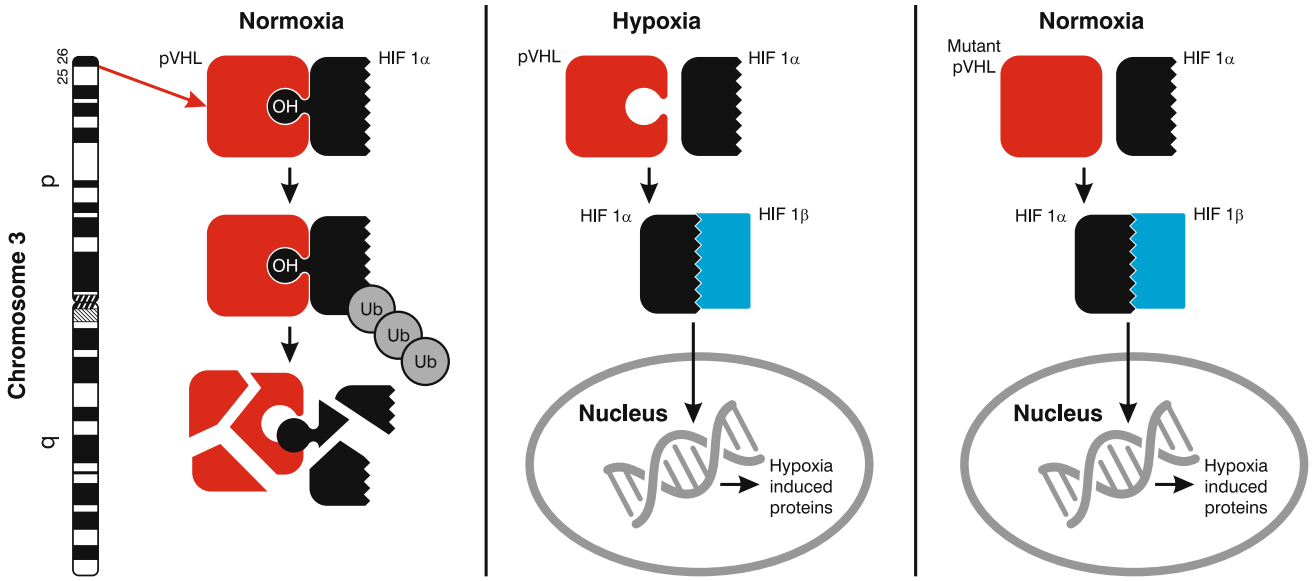

Fig. 1 Regulation of hypoxia-induced cellular response as a consequence of the mutation to both copies of VHL gene

the formation of aggressive, type 2 pRCC. Birt–Hogg–Dube syndrome, an effect of BHD gene mutation on the chromosome 17, can cause susceptibility to chromophobe RCC (cRCC), oncocytoma, and ccRCC [4].

Metastatic RCC

Surgical removal of the localized renal tumor, in some cases combined with metastasectomy, remains the only curative treatment for RCC. Patients with advanced disease might benefit from modern systemic therapy, which has contributed towards a better understanding of RCC biology and carcinogenesis.

Approximately 20–30% of patients present initially with metastatic disease and an additional 20% will progress after radical surgical treatment [10, 11]. This recurrence rate justifies follow-up after treatment. However, there is no clear data concerning its benefit. Also, there is no consensus regarding the optimal surveillance algorithm following treatment for RCC [5].

Risk of developing metastases after radical treatment can be assessed using nomograms and scoring systems incorporating pathologic stage, tumor size, the status of lymph nodes, and the presence of necrosis. Table 1 shows an exemplary prognostic model.

According to the analysis of 11,157 patients with metastatic RCC, lungs are the most common metastatic site and are affected in 45% of cases. Therefore, adequate surveillance, apart from abdomen-CT, should also include chest-CT. Pulmonary metastases are followed by bones (30%), lymph nodes (28%), liver (20%), adrenals (9%), brain (8%), peritoneum (7%), and gastrointestinal tract and pleura (3%). Other locations are rare. Sixty-one percent of patients will develop monometastatic disease and 39% polimetastatic disease, with a predominance of polimetastatic disease among younger patients. Bones and brain metastases are very often accompanied by other locations [13].

Metastatic RCC is a heterogeneous group in terms of prognosis of total survival. Various prognostic models have been developed, with Memorial Sloan Kettering Cancer Center (MSKCC) and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) being most commonly used. Table 2 compares two RCC prognostic models and the variables that are being evaluated. Discrepancies should be noted in defining risk group.

There is inconsistency in defining the risk groups between the two models. It is estimated that 54.1% of patients within the MSKCC poor risk group are assigned to an IMDC intermediate risk group, and 20.2% of patients of the MSKCC intermediate risk group are assigned to the favorable IMDC risk group [18].

Treatment

In the last decade, remarkable progress has been observed in the treatment of metastatic RCC. Interferon and Interleukins 2, drugs acting nonspecifically on cytokines, have been the mainstay of systemic therapy. These drugs were gradually replaced by tyrosine kinase inhibitors (TKI) and threonine–serine inhibitors (mTOR inhibitors). Due to increased interest in immunotherapy and the discovery of the mechanisms controlling immunological response and

Table 1 Risk of developing metastases after radical treatment for RCC [12]

Variables	Score
TNM stage	
pT1a	0
pT1b	2
pT2	3
pt3a-T4	4
Regional lymph nodes	
pNx and pN0	0
pN1–2	2
Tumor size	
< 10 cm	0
≥ 10 cm	1
Fuhrman grade	
G 1–2	0
G 3	1
G 4	3
Tumor necrosis	
No	0
Yes	1

Score	Group	5-year metastasis-free survival (%)
0–2	Low risk	97.1
3–5	Intermediate risk	73.8
≥ 6	High risk	31.2

Table 2 MSKCC and IMDC prognostic models

Variable	MSKCC	IMDC
Karnofsky performance status < 80%	0–1	0–1
Time from diagnosis to systemic treatment < 1 year	0–1	0–1
Hemoglobin < LLN	0–1	0–1
LDH > 1.5 × ULN	0–1	–
Calcium > 10 mg/dL (> 2.5 mmol/L)	0–1	0–1
PLT > ULN	–	0–1
NEUT > ULN	–	0–1

Table 3 Prognoses of patients with metastatic RCC by MSKCC and IMDC models [14–17]

Risk group	% of patients	Number of risk factors	Median survival [months]
Memorial sloan kettering cancer center prognostic model			
Favorable	18	0	29
Intermediate	62	1–2	14
Poor	12	3–5	4
International metastatic renal cell carcinoma database consortium prognostic model			
Favorable	18	0	43
Intermediate	52	1–2	27
Poor	30	3–6	8.8

interaction between a cancer cell and the immune system, immune checkpoint inhibitors have also been introduced (Table 3).

Apart from suppression of overexpressed VEGF and PDGF pathways, tyrosine kinase inhibitors are also acting on other kinases, which are associated with carcinogenesis. Cabozantinib, an oral inhibitor of TK, is characterized by a particularly broad spectrum of activity. Cabozantinib inhibits various tyrosine kinases, including VEGF, MET, GAS6 (AXL), RET, ROS1, TYRO3, KIT, TRKB, FLT3, and TIE-2. This diversity implicates a possibility to overcome resistance to treatment with TKI with a narrower spectrum of activity.

Threonine–serine kinase inhibitors of mTOR (mammalian target of rapamycin) were also introduced into clinical practice. mTOR activity is increased in malignancies and inhibition of its signaling interferes with proteins that participate in the cell cycle, angiogenesis, and glycolysis. Therefore, in addition to glucose metabolism, mTOR inhibitors

suppress proliferation of the tumor, endothelial cells, fibroblasts, and blood vessels smooth muscles.

Modern immunotherapy, which targets the interaction of programmed cell death protein 1 (PD-1) with its ligands PD-L1 and PD-L2, showed great promise. Inhibition of the interaction between these proteins leads to the increased cytotoxic response of the immune system against the neoplastic tissue.

Surgical excision of metastases in comparison to systematic treatment was shown to be significantly more effective, offering a chance to cure. Therefore, if technically feasible, metastasectomy should be offered to the patients with mono and oligometastatic disease.

Surgical treatment and radiosurgery

In the uro-oncologic community, there is an ongoing debate on the importance of the surgical treatment of primary tumor in patients with locally advanced and metastatic disease. Radical surgical treatment is not feasible in the vast majority of patients with metastatic disease and the significance of primary tumor removal remains questionable.

A meta-analysis by Flanigan et al. which included 331 patients, demonstrated that the median overall survival in patients who underwent radical nephrectomy with subsequent interferon treatment was 13.6 months, in comparison to 7.8 months for those treated only with interferon [19]. Nevertheless, systemic monotherapy with interferon is no longer valid.

The role of cytoreductive nephrectomy (CN) before molecular guided systemic therapy has been debatable. Therefore, a downward trend in the number of performed CNs before systemic therapy has been observed [20]. Retrospective analysis of 1658 patients with metastatic RCC, based on data from the IMDC study, demonstrated that the median survival in patients who underwent operation was 20.6 months, in contrast to 9.5 months in the non-operated group. It should be noted that patients with a better prognosis have been qualified more often for CN. However, after the inclusion of IMDC prognostic factors, the benefit of cytoreductive treatment persisted. The results of the prospective CARMENA study were announced during the American Society of Clinical Oncology annual meeting in June 2018. The study authors demonstrated non-inferiority in overall survival in patients within the intermediate and poor prognosis risk groups initiating systemic therapy with sunitinib without prior CN. Limitations of this study include its non-inferiority character and the fact that a substantial number of the included patients belong to the poor prognosis risk group. This raises doubt about the suitability of CN in combination with immunologic treatment [21].

Local treatment of RCC metastases, whether surgical or with radiation therapy, remains an important yet controversial procedure. It is agreed that after initial radical treatment, 17–19% of patients with the emergence of metastatic lesions can be cured [22, 23]. Most studies investigate the results of surgical treatment of pulmonary metastases. The 5- and 10-year survivals after pulmonary metastasectomy are 31–60% and 33%, respectively [24–29]. After pulmonary metastasectomy, no adjuvant systemic therapy is initiated [5].

The most effective therapy for brain metastases is stereotactic radiotherapy, which allows achieving local control for at least 1 year in 84% of patients and 94% of patients in conjunction with surgical treatment [30].

Systemic therapy for renal cell carcinoma

Systemic therapy for RCC includes bevacizumab in combination with interferon alfa (IFNα), tyrosine kinase inhibitors, serine–threonine kinase inhibitors mTOR, and immunocompetent drugs. Cytostatic treatment can be implemented in only limited cases. Figure 2 features drugs approved in the treatment of metastatic RCC and their mechanism of action.

Molecular targeted therapy

Research on the influence of VHL protein and increased angiogenesis on the RCC cancerogenesis contributed to significant progress in the treatment of RCC and the development of targeted therapy.

Vascular endothelial growth factor (VEGF) inhibition

Bevacizumab, a recombinant humanized monoclonal antibody, is approved in the treatment of metastatic RCC. Bevacizumab blocks angiogenesis by inhibition of VEGF binding with its surface receptors on the vascular endothelium, suppressing the development of various solid tumors including RCC.

The efficacy and safety of bevacizumab in combination with interferon alfa as a first-line treatment were evaluated in the AVOREN phase III study. Patients with dominant ccRCC were included in this study. Interferon alfa-2a monotherapy was compared with the bevacizumab–interferon combination therapy. Improvement in progression-free survival and no effect on total survival were demonstrated [31]. These results are consistent with the findings of the CALGB90206 study [32]. According to drug registration,

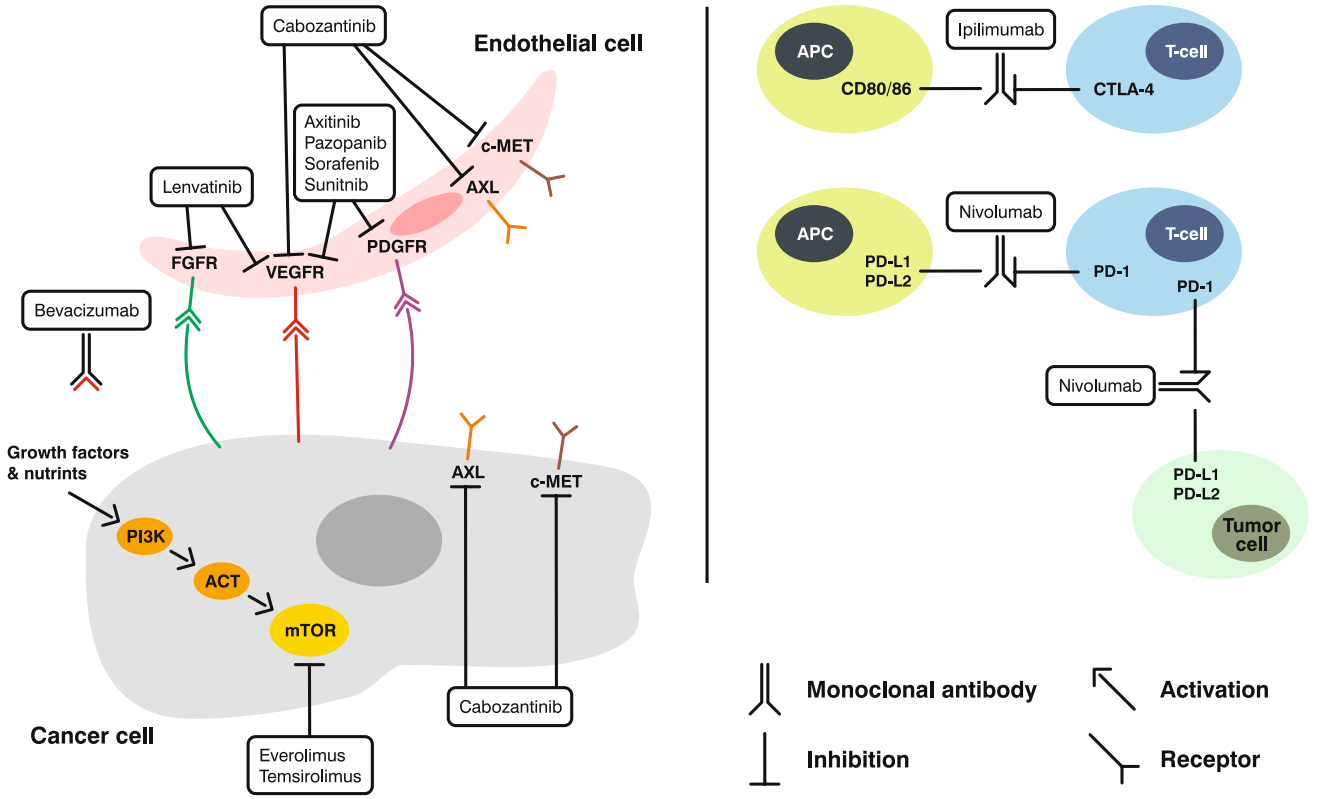

Fig. 2 Drugs approved in the treatment of metastatic RCC: mechanisms of action

bevacizumab–interferon alfa-2a combination is approved in the first-line treatment of advanced and metastatic RCC.

Tyrosine kinase inhibitors (TKI)

Transmission of the cellular signal is dependent on the presence of receptor proteins. In response to the exposure of surface receptors from extracellular molecules, secondary messengers are activated by phosphorylation. Overstimulation of tyrosine kinase might lead to uncontrolled proliferation and generation of metastases. Tyrosine kinase inhibitors are low molecular weight compounds that inhibit a second messenger system. Seven different kinase inhibitors are significant in the treatment of RCC: sorafenib, sunitinib, pazopanib, axitinib, tivozanib, lenvatinib, and cabozantinib. Biologically, these differ with respect to their strength and spectrum of inhibition, which translates directly into antitumor activity and potential side effects.

Early experiences with sorafenib, a kinase inhibitor, were disappointing. Studies comparing interferon alfa-2a with sorafenib demonstrated no difference in progression-free survival and total survival [33]. However, the TARGET study (which compared sorafenib with placebo) reported benefit in progression-free survival and no effect on total survival in patients resistant to cytokine therapy. After considering that sorafenib was introduced after cancer progression, a statistically significant benefit in overall survival was detected [34]. Sorafenib is approved for the "treatment of patients with advanced renal cell carcinoma (RCC) who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy."

Sunitinib has proven to be a more potent TKI. A study comparing the effectiveness of the first-line treatment of sunitinib with IFNα demonstrated superiority in median overall survival in a group receiving sunitinib, however, with borderline statistical significance ($p=0.051$). Median progression-free survival was significantly higher in the sunitinib group [35, 36]. Moreover, a meta-analysis from 2015 showed that first-line treatment with sunitinib prolonged median progression-free survival more than bevacizumab–IFNα, everolimus, sorafenib, and temsirolimus–bevacizumab. No difference in PFS was reported between sunitinib, axitinib, pazopanib, and tivozanib [37].

So far, sunitinib is the only drug used in adjuvant therapy after radical surgical treatment in patients with high risk of recurrence. The S-TRACK study demonstrated that sunitinib prolongs median progression-free survival to 6.8 years in comparison to 5.6 years in patients receiving placebo. No unequivocal data exist regarding overall survival [38]. On

the other hand, the three-arm ASSURE study, where adjuvant therapy with sunitinib or sorafenib was compared to placebo, no differences in progression-free survival or overall survival were detected. No subpopulation was specified, which would benefit from such treatment [39]. The authors of the S-TRACK study explain discrepancies between results by citing the central evaluation of CT scans in the S-TRACK study and more restrictive inclusion criteria, narrowing the study group to high-risk patients with ccRCC only [38]. Based on the results from the S-TRACK study, sunitinib was FDA-approved for the "adjuvant treatment of adult patients at high risk of recurrent renal cell carcinoma following nephrectomy." In Europe, sunitinib is only approved in the treatment of advanced and metastatic RCC in adult patients.

Pazopanib is another drug from the TKI family. A phase III study comparing the effectiveness of pazopanib vs. placebo in the first- and second-line treatment after initial cytokine therapy demonstrated benefit in progression-free survival. In subpopulations without neoadjuvant therapy, as well as initially treated with cytokines, differences in PFS were statistically significant (2.8 vs. 11.1 and 4.2 vs. 7.4, respectively) [40]. Further studies comparing pazopanib and sunitinib showed the similar effectiveness of both drugs with superior tolerability of pazopanib [41, 42]. Nonetheless, no advantage in adjuvant treatment with pazopanib after radical treatment was demonstrated [43].

Axitinib is a second generation TKI with 50–450 times greater affinity for VEGF receptors in comparison to older TKI's and is considered a subsequent-line treatment for RCC. A study comparing the effectiveness of axitinib versus sorafenib in patients after failure of first-line systemic treatment demonstrated that axitinib significantly prolongs median progression-free survival with no effect on overall survival [44].

Another study by Motzer et al. comparing tivozanib vs. sorafenib in initial therapy and after the failure of the first-line treatment, detected noticeable prolongation of PFS in the tivozanib arm. On the other hand, overall survival was longer in the sorafenib arm (median overall survival: 29.3 vs. 28.8 months). Limitations of the study included the fact that patients in good health more often received sorafenib and, after initial treatment failure with sorafenib, they received tivozanib [45]. Therefore, tivozanib did not receive approval in the USA. However, the European Medical Agency approved tivozanib for the "first-line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are VEGFR and mTOR pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced RCC."

Long-term treatment with VEGF receptor inhibitors results in overexpression of collateral pathways, leading to progression of the disease. Understanding this mechanism leads to the development of new, broader spectrum acting TKIs. Lenvatinib is a tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF) receptors and fibroblast growth factor receptors (FGFR). A combination therapy of lenvatinib with everolimus (mTOR inhibitor) was demonstrated to be more effective in the treatment of the patients after progression with VEGF signaling-guided treatment vs. monotherapy with lenvatinib or everolimus [46].

Cabozantinib is a VEGF, AXL, and MET kinase receptor inhibitor. AXL and MET receptors are associated with resistance to VEGF signaling-targeted treatment. A study comparing the effectiveness of treatment with cabozantinib versus everolimus after progression on classical VEGF signaling kinase inhibitors demonstrated longer median progression-free and overall survival in the cabozantinib arm [47]. As a result of its high efficiency, a study evaluating the effectiveness of cabozantinib versus sunitinib for patients with metastatic RCC of poor or intermediate risk was conducted. Prolongation of progression-free survival was demonstrated but no mature data regarding overall survival are available [48]. Cabozantinib granted FDA and EMA approval for first-line treatment and patients with disease progression following prior anti-VEGF therapy.

Threonine–serine kinase inhibitors (STK inhibitors): mTOR

STK inhibitors are a group of drugs inhibiting mTOR kinase, which controls cellular division. Inhibition of mTOR activity results in suppression of cancer growth by blocking protein translation, which regulates the cellular cycle. The process of protein synthesis and cellular division is disrupted through inhibition of phosphorylation and activation of 4E-BP1 and S6K proteins. Furthermore, the mTOR kinase might regulate translation of hypoxia-inducible factor 1 and 2, thus decreasing adaptation of the neoplasm to hypoxia and suppressing angiogenesis by inhibition of the production of VEGFs [49].

Temsirolimus was the first STK inhibitor approved for treatment of RCC. A study conducted by Hudges at al. evaluated the effectiveness of temsirolimus in patients with poor prognosis RCC. Participants were assigned into groups receiving temsirolimus, IFN-α, or a combination of both. The median progression-free survival and overall survival were highest in patients receiving temsirolimus [50]. Based on the results of this study, temsirolimus was approved in the European Union for the "first-line treatment of patients with advanced renal cell carcinoma (RCC) who have at least three of six prognostic risk factors."

By contrast, a study evaluating the effectiveness of treatment with everolimus versus placebo after initial treatment failure with sunitinib, sorafenib, or both demonstrated prolongation of progression-free survival and no difference in

overall survival in patients treated with everolimus [51]. According to drug approval registry, everolimus is approved for "treatment of patients with metastatic renal cell carcinoma (mRCC) after the failure of a previous vascular endothelial growth factor (VEGF)—targeted agent."

Immunotherapy

Infiltration of T lymphocytes inside the tumor [52] together with the single cases of spontaneous regression of metastatic disease suggests that RCC is a highly immunogenic type of cancer. This observation initiated the development of immunologic therapy.

Cytokine-based immunotherapy with IFN-α or IL-2 turned out to be an effective therapeutic option for a small subgroup of patients with metastatic RCC. The theoretical basis for the treatment with IFN-α is its multi-directional actions: direct antiproliferative and antiangiogenic properties, stimulation of the lytic activity of lymphocytes NK, and the expression of various antigens, including class I HLA antigens on the surface of the cancer cells. As a consequence, tumor cells are recognized and killed by cytotoxic T lymphocytes. A randomized study by the Medical Research Council demonstrated that monotherapy with interferon prolongs median overall survival by 2.5 months in comparison to medroxyprogesterone [53]. Currently, with the availability of more effective treatment, monotherapy with IFN-α is considered obsolete.

Interleukin-2 (IL-2), a cytokine, is the most important lymphocyte T growth factor. Based on the results of seven, phase II, multicenter studies, high dose therapy with IL-2 (HD IL-2) was approved by the Food and Drug Administration (FDA) for treatment of metastatic RCC. According to the most recent analysis, 15% of patients achieve therapeutic response with HD IL-2. The median duration of response lasts 54 months. In 7% of patients, a full remission is observed, which is maintained for 3–131 months (median, 80 months) [54].

Our understanding of the basic control mechanisms that regulate the activation of the immune cells, especially T-cells, has improved significantly in recent years. Programmed death receptor 1 (PD-1), a protein from the CD28 family, regulates the function of lymphocytes T and plays a major role in the escape from the control of the immune system. Interaction of the PD 1 receptor with its ligand (PD-L1) on the cancer cell inhibits proliferation of lymphocyte T, its cytotoxic properties, and the release of cytokines. This leads to the programmed death of cancer-specific T-cells. Lymphocyte differentiation to regulatory T-cells is facilitated, and resistance to attack from cytotoxic cells is increased [55].

Nivolumab, a humanized IgG4 antibody against the PD-1 receptor, is a drug of a major significance in the treatment of metastatic RCC. Its mechanism of action includes blocking of the PD-1 receptor, thus allowing T-cells to work. A randomized study comparing the effectiveness of everolimus vs. nivolumab in patients with progression of RCC after the first- or second-line antiangiogenic treatment demonstrated more frequent therapeutic response (25% vs. 5%) and lower death risk in the group receiving nivolumab. Superior therapeutic results with nivolumab persisted independently of the presence of PD-L1 expression in the primal tumor. Moreover, grade 3 or grade 4 side effects were less common in the group receiving nivolumab. Significant and constant improvement of the median quality of life during the 2-year period of treatment with nivolumab has been demonstrated [56]. Based on this study, nivolumab has been approved in Europe in monotherapy after prior therapy of advanced RCC in adult patients. Based on the promising results of the modern immunotherapy in the treatment of the patients who progressed after therapy with kinase inhibitors, further research was needed to evaluate the effectiveness of nivolumab in the first-line setting. A study comparing the effectiveness of combination therapy of nivolumab and ipilimumab in metastatic RCC showed that patients with intermediate and poor prognosis who underwent immunotherapy had better outcomes. However, patients with a good prognosis would benefit more from the treatment with sunitinib [57]. Currently, many studies are being conducted evaluating the role of immunotherapy in adjuvant therapy, on the role of other immunocompetent drugs in the treatment of RCC (pembrolizumab, atezolizumab, avelumab), and on the combination of immunocompetent drugs with antiangiogenic drugs, as well as on the use of immunotherapy in the treatment of patients with non-clear cell RCC.

Summary of therapeutic options in the treatment of metastatic RCC

Table 4 summarizes the results of randomized trials with drugs registered for the treatment of renal cell carcinoma.

Special clinical situations

In some clinical situations, there are doubts concerning the effectiveness of the systemic treatment. This applies to patients with a different histopathological variant, i.e., non-clear cell RCC, neoplasms with distinct biology. Another example is central nervous system metastases, where penetration of drugs is limited due to the brain–blood barrier.

Patients with non-clear cell RCC constitute a minority of patients with renal cancer. Because of the rarity of other

Table 4 Summary of studies evaluating the effectiveness of the FDA- or EMA-approved drugs in the first- and further-line treatment

	DFS [years]	OS [years]
Adjuvant therapy		
Sunitinib[a] versus Placebo [38]	6.8 vs. 5.6 ($p=0.03$)	–
	PFS [months]	OS [months]
Palliative treatment—first-line treatment		
Pazopanib[a,b] versus Placebo [40]	9.2 vs. 4.2 ($p<0.001$)	22.9 vs. 20.5 ($p=0.224$)
Bevacizumab + IFN-α [a,b] versus IFN-α (two studies) [31, 32]	10.2 vs. 5.4 ($p<0.001$)	23.3 vs. 21.3 ($p=0.13$)
	8.5 vs. 5.2 ($p<0.001$)	18.3 vs. 17.4 ($p<0.001$)
Sunitinib versus Pazopanib	9.5 vs. 8.4 (NR)	29.1 vs. 28.3 ($p=0.24$)
Temsirolimus [a,b] versus Temsirolimus and IFN-α versus IFN-α [50]	5.5 vs. 4.7 vs. 3.1 ($p<0.001$*)	10.9 vs. 8.4 vs. 7.3 ($p=0.07$*)
Tivozanib[b] versus Sorafenib [45]	11.9 vs. 9.1 ($p=0.042$)	20.1 vs. 19.2 ($p=0.152$)
Ipilimumab with nivolumab[a] versus Sunitinib (intermediate/poor risk) [57]	11.6 vs. 8.4 ($p=0.0331$**)	NR vs. 26.0 ($p<0.0001$)
Cabozantinib[a,b] versus Sunitinib (intermediate/poor risk) [48]	8.6 vs. 5.3 ($p=0.0008$)	26.6 vs. 21.2***
Palliative treatment—second- and further-line treatment		
Everolimus[a,b] versus Placebo [51]	4.9 vs. 1.9 ($p<0.001$)	14.8 vs. 14.4 ($p=0.162$)
Sorafenib[a,b] versus Placebo (after immunotherapy) [34]	5.5 vs. 2.8 ($p<0.01$)	17.8 vs. 15.2 ($p=0.146$)
Axitinib versus Sorafenib [44]	6.7 vs. 4.7 ($p<0.001$)	20.1 vs. 19.2 ($p=0.3744$)
Lenvatinib with everolimus[a,b] versus Lenvatinib vs. everolimus [46]	12.8 vs. 9.0 vs. 5.6 ($p=0.003$****)	25.5 vs. 19.1 vs. 15.4 ($p=0.02$****)
Cabozantinib[a,b] versus everolimus [47]	7.4 vs. 3.2 ($p<0.001$)	21.4 vs. 16.5 ($p=0.003$)
Nivolumab[a,b] versus everolimus [56]	4.6 vs. 4.4 ($p<0.11$)	25.0 vs. 19.6 ($p=0.002$)

PFS progression-free survival, *OS* overall survival

*For temsirolimus versus IFN-α

**Non significant

***Immature data

****For lenvatinib with everolimus

[a]FDA approved

[b]EMA approved

histological variants, conducting phase III studies to address this is challenging. Moreover, the dominant pathological pattern in the majority of studies is ccRCC. The study with temsirolimus is one exception. In the registration phase III study, 20% of patients had histology different than ccRCC. It was demonstrated that patients with non-clear cell RCC, in comparison to interferon, benefit from treatment with temsirolimus. Additional data concerning treatment of those patients come from expanded access trials. An expanded access trial with sunitinib demonstrated that 68% of patients with non-clear cell RCC would achieve clinical benefit (defined as a therapeutic response or disease stabilization). Independently of histology, 76% of patients with RCC achieved clinical benefit. By contrast, sorafenib is associated with clinical benefit in 90% of patients with chromophobe RCC and 84% of patients with papillary RCC. Comparison of the results from both studies is impossible due to differences in endpoints [58, 59].

According to the analysis of over 11,000 of patients, brain metastases are estimated to account for approximately 8% of all RCC metastases. Moreover, in the majority of cases, it coexists with metastasis in a different location, rather than occurring alone. Kinase inhibitors cross the brain–blood barrier in a limited manner [60]. It seems that treatment with kinase inhibitors partially protects the population of patients with metastatic RCC from the occurrence of metastases in the central nervous system [61]. Expanded access trials demonstrate a clinical benefit (64% vs. 77%) in patients treated with sunitinib with and without brain metastases, respectively. In comparison, 72% of patients with brain metastasis treated with sorafenib positively responded to treatment [58, 59].

Conclusions

Radical tumor resection is a mainstay treatment for RCC. Metastatic disease that is non-feasible for surgical treatment remains incurable. Numerous studies have demonstrated that—with the introduction of new drugs—the treatment

outcomes of metastatic RCC have improved [62]. The development of new therapies as well as the optimization and individualization of procedures allow us to hope for further progress in this area.

Compliance with ethical standards

Conflict of interest Pawel Wiechno has received speakers' honoraria and travel grants from Pfizer, Bayer, Novartis, and IPSEN. Jakub Kucharz has received research grant from Novartis, travel grants and speakers' honoraria from Pfizer, Bayer, Novartis, and IPSEN. Other authors declare no conflicts of interest.

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