Chapter e161: Renal Cell Carcinoma

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KEY CONCEPTS

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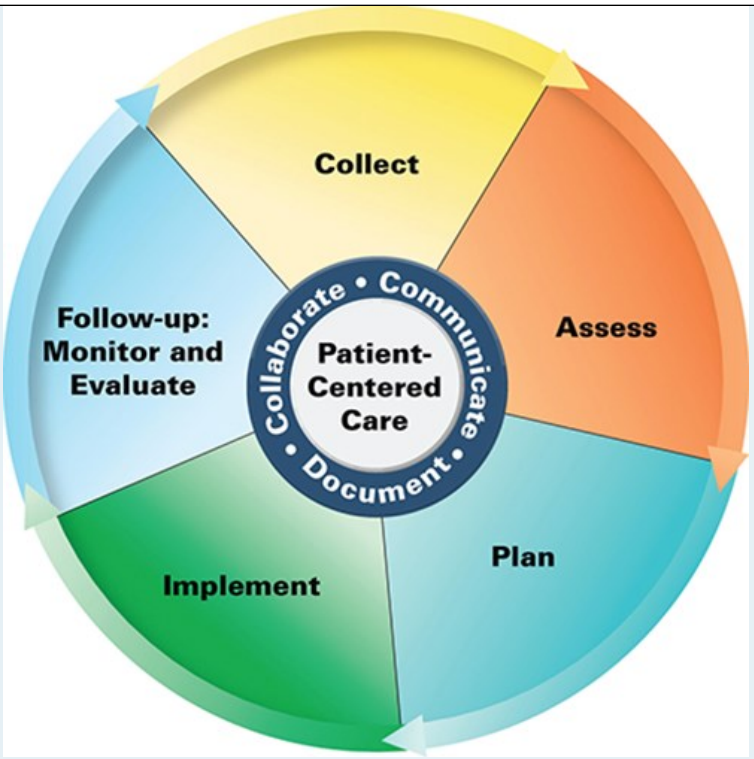
1. Renal cell carcinoma (RCC) predominantly occurs later in life, with about 70% of all cases diagnosed between the ages of 55 and 84 years.
2. Established risk factors for RCC include smoking, obesity, hypertension, and inherited susceptibility.
3. Inactivation of the von Hippel-Lindau tumor suppressor gene (*VHL*) is the hallmark of the most common type of RCC, the clear cell histologic subtype.
4. More than 50% of RCC cases are diagnosed by incidental findings on routine imaging for unrelated reasons.
5. The Memorial Sloan-Kettering Cancer Center (MSKCC) Prognostic Factors Model for Survival and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Criteria classifies patients into favorable-, intermediate-, and poor-risk groups based on clinical factors, and can predict survival among both untreated patients and those treated with immunotherapy and/or targeted agents.
6. Surgical excision of the primary tumor, either by radical or partial nephrectomy, is the preferred treatment modality for patients with stage I-III RCC, but some patients with stage IV disease may also benefit from surgery.
7. Immunotherapy (programmed cell death protein-1 [PD-1], PD-ligand 1 [PD-L1] and cytotoxic T lymphocyte-associated antigen-4 [CTLA-4] inhibitors) and targeted therapy (multikinase inhibitors, mammalian target of rapamycin [mTOR] inhibitors, and vascular endothelial growth factor [VEGF] inhibitors) are integral components of the management of advanced or metastatic RCC with unique mechanisms of action and adverse drug reaction profiles.
8. First-line treatment options for metastatic RCC (mRCC) are chosen based on patient-specific factors and include small molecule tyrosine kinase inhibitors (sunitinib, pazopanib, axitinib, cabozantinib), an mTOR inhibitor (temsirolimus), and immune checkpoint inhibitor combinations (ipilimumab plus nivolumab, nivolumab plus cabozantinib, pembrolizumab plus axitinib, and pembrolizumab plus lenvatinib).
9. In patients who progress after first-line treatment, multikinase inhibitors cabozantinib, axitinib, and lenvatinib (in combination with everolimus) or immunotherapy with nivolumab may be considered. Combination of nivolumab and ipilimumab and combination immunotherapy with a multikinase inhibitor (eg, pembrolizumab plus axitinib) are also options. A multikinase inhibitor, tivozanib, is an option for patients who have received two or more prior therapies.

PATIENT CARE PROCESS

Patient Care Process for Renal Cell Carcinoma



Collect

- Patient characteristics (age, weight, height and past medical history)
- Laboratory assessment with a complete blood count (CBC), comprehensive metabolic panel, liver function tests (LFTs), and lactate dehydrogenase (LDH), and calculate the corrected calcium
- Social history (including tobacco and alcohol use) and family history (including cancer history)
- A comprehensive medication list that includes prescribed and over-the-counter medications, herbal remedies, dietary supplements, and vitamins
- Additional information pertinent to patient prognosis (see Table e161-3)

Assess

- Tumor staging based on TNM criteria and histology (see Tables e161-1 and e161-2) and performance status to evaluate the ability to undergo treatment
- Patient prognostic risk score by IMDC or MSKCC criteria (see Table e161-3)
- Potential moderate and serious drug-drug interactions (see Table e161-4)

Plan*

- Treatment selection, which includes dose, route, frequency, and duration
- Establish monitoring parameters, frequency of monitoring, and plan for follow-up in clinic
- Coordination of medication acquisition with insurance, specialty pharmacy, and in certain situations with the pharmaceutical industry (eg, free drug for indigent patients)

- Medication administration education and determine barriers to adherence for orally administered targeted therapies

Implement

- Patient education on all facets of the treatment plan, including management of adverse drug reactions. For immunotherapies, patient education will also include when to contact providers (instead of self-care) should adverse drug reactions arise.
- For orally administered targeted therapies, educate on administration, handling precautions, medication adherence, and also processes and procedures with specialty pharmacy.
- Schedule follow-up labs (eg, CBC, comprehensive metabolic panel, LFTs), and schedule appointment for adverse drug reaction and adherence assessment.

Follow-Up

- Follow-up frequency following pharmacotherapy initiation should be tailored to the medication-specific monitoring requirements and incidence and severity of treatment-related adverse drug reactions (see Table e161-5). Additional follow-up may be required for monitoring the effects of drug-drug interactions.
- Efficacy monitoring is based on serial imaging results. Frequency of imaging can range between 6 and 16 weeks, and may be dependent on patient-specific clinical factors, cancer-related symptoms, rate of cancer progression, and type of therapy received.

Monitor:

- Monthly physical exam to evaluate the recurrence of disease-related symptoms and treatment-related adverse drug reactions
- Monthly monitoring of medication adherence to regimens containing orally administered targeted therapies

Evaluate:

- Monthly evaluation of laboratory values to monitor disease response and/or treatment-related adverse drug reactions. Laboratory monitoring is medication specific and may be more frequent following treatment initiation or while managing laboratory-related adverse events.
- Evaluation of imaging studies (computed tomography [CT], positron emission tomography [PET], magnetic resonance imaging [MRI]) every 6 to 16 weeks to monitor disease response, stabilization, or progression. Treatment is continued with response or stable disease.

**Collaborate with patients, caregivers, and other healthcare professionals.*

BEYOND THE BOOK

BEYOND THE BOOK

Develop a study table showing appropriate first-line treatment options for advanced and metastatic clear cell RCC in different patient groups. This summary table should include factors included in the MSKCC and IMDC Criteria prognostic scoring tools. The summary table should also include how these prognostic tools stratify patients into favorable/low-, intermediate-, and poor-risk categories. This summary table should include both orally and intravenously administered pharmacotherapeutic options. The intent of this activity is to help students practice their skills in the Collect and Assess steps of the patient care process and apply them to patients with advanced and metastatic RCC.

INTRODUCTION

Renal cell carcinoma (RCC) represents about 2% to 4% of all adult malignancies and is the most common type of malignancy of the kidney and renal

pelvis. Few treatment options existed, and those that were available had modest activity and were poorly tolerated by patients. However, treatment for the disease has been revolutionized by targeted agents and immunotherapies that were developed based on an increased understanding of RCC pathophysiology. Clear cell is the predominant histologic subtype of RCC (about 80% of all cases) and is characterized by the inactivation of the von Hippel-Lindau (*VHL*) tumor suppressor gene located on chromosome 3p25. *VHL* inactivation leads to increased production of growth factors, such as vascular endothelial growth factor (VEGF), transforming growth factor (TGF), platelet-derived growth factor (PDGF), and others responsible for angiogenesis and cell growth.[1] Several targeted drugs have been approved as first- or subsequent-line therapy for RCC in recent years.[2–11] Each drug is an example of targeted therapy against growth factors important in the pathophysiology of RCC, and has yielded much needed progress in a disease with few therapeutic options. Additionally, immune checkpoint inhibitors, such as avelumab, ipilimumab, nivolumab, and pembrolizumab, have emerged as treatment options, with novel mechanisms of action and adverse drug reaction profiles. Immune checkpoint inhibitors work by amplifying T-cell response against tumor-specific antigens. RCC serves as an example of the rational development of targeted agents based on knowledge of tumor biology and molecular signaling pathways for the treatment of other malignancies.

EPIDEMIOLOGY

In this chapter, the term “women” and “men” are used to reflect gender identified in previous research studies and other literature on kidney cancer and to recognize the biological sex of individuals at birth. In doing so, we recognize that not all patients with kidney cancer identify as females or males at the time of diagnosis and treatment of kidney cancer. About 79,000 new cases of kidney and renal pelvis cancer are diagnosed each year in the United States, with almost two-thirds of these cases occurring in men.[12] Nearly 14,000 people in the United States die of kidney cancer each year.[12] Kidney cancer is the sixth most common cancer in men, and the number of new cases diagnosed each year is similar to non-Hodgkin lymphoma and cancers of the head and neck. In women, kidney cancer is the eighth most common cancer, occurring at a rate similar to the rates for leukemias and pancreatic cancers.[12] The incidence of RCC has increased over the past three decades, although the rates of death have been falling an average of 1.4% between 2009 and 2018. The incidence of RCC has increased more rapidly in Black individuals than White individuals and more rapidly in women than men, although rates in women appear to have stabilized in recent years. In the United States, between 2013 and 2017, the age-adjusted incidence rate in Black men was 24.5, White men 23.0, Black women 12.2, and White women 11.4 per 100,000 person-years.[13] This increase may be related to improved imaging techniques and greater use of these imaging modalities, although the higher prevalence of some risk factors may also explain the increased incidence.

1 Kidney cancer is most commonly diagnosed between the ages of 55 and 74 years, with a peak in the sixth and seventh decades of life.[13] Nearly 70% of all cases of kidney cancer are diagnosed in people between the ages of 55 and 84 years, with around 3% of all cases diagnosed in patients younger than 34 years. The median age at diagnosis is 64 years old.[13]

One of the primary factors influencing overall survival is the extent of disease spread. When the tumor is confined to the kidney at the time of diagnosis, surgical resection can result in a five-year overall survival of about 93%.[12] However, that figure falls to 71% when localized spread has occurred beyond the kidney.[12] Approximately 20% to 30% of patients with localized disease will relapse within three years following surgery, and about 30% of RCC patients will present initially with metastatic disease.[13] The five-year survival rate for patients diagnosed with metastatic disease is about 14%.[13] Median overall survival for RCC has improved over the past two decades, which could be attributed to improved screening and early detection of smaller tumors, the use of cytoreductive nephrectomy prior to the use of systemic therapy in advanced disease, or the availability of multiple new agents that target angiogenic, immunogenic, and oncogenic signaling pathways.

ETIOLOGY

The incidence rates of RCC vary more than 15-fold worldwide, with the highest incidence rates in the more developed regions of North America, Europe, and Australia and the lowest in Africa and Asia, which suggests that lifestyle and environment could be important factors underlying the development of RCC.[14] Established risk factors associated with RCC include smoking, obesity, hypertension, and inherited susceptibility.[14,15]

2 Smoking remains the most consistently established risk factor and is responsible for 10% to 30% of RCC diagnoses.[14] Smoking is associated with a relative risk of 1.54 for men and 1.22 for women, with a strong dose-dependent relationship. Heavy smoking, defined as 21 or more cigarettes per day, increases the relative risk (2.03 and 1.58, respectively). Smoking cessation reduces the risk of RCC, with a 15% to 30% decrease in patients who have

quit smoking for 10 to 15 years, and a 50% decrease for those who have quit for 30 years or more.[16]

Obesity is also an established risk factor in RCC, based on multiple prospective cohort studies. A large cohort study that included over nine million participants and 15,000 cases of kidney cancer found an increased relative risk of 1.77 in participants who were obese (BMI greater than 30 kg/m^2), and an increased relative risk of 1.28 in those who were overweight (BMI 25-29.99 kg/m^2). The risk of kidney cancer increases linearly with increasing BMI, with a 4% increased risk for every 1 kg/m^2 increase in BMI.[17] About 30% to 40% of RCC cases may be attributed to obesity, which suggests that increasing rates of obesity in the United States may be partially responsible for the increased incidence of RCC observed over the past three decades.[18] Numerous mechanisms that could explain the link between obesity and RCC development have been proposed, but none have yet been definitively validated. One plausible hypothesis has linked obesity to increased lipid peroxidation, which can result in carcinogenesis of the proximal renal tubules. Byproducts of the lipid peroxidation pathway can result in deoxyribonucleic acid (DNA) adducts in the kidney, which lead to oncogene and tumor suppressor gene mutations, and eventually to malignancy.[19] In addition, adipose tissue impacts the metabolism and endocrine environment in the body. Increased adipose tissue can lead to chronic states of inflammation, increased insulin and insulin-growth factor 1, and increased estrogen and decreased adiponectin, all of which are associated with tumorigenesis.[20] Finally, the kidneys of obese men and women are more susceptible to carcinogenesis because of higher glomerular filtration rates, increased renal perfusion, and atrophic scarring of the kidneys.[18]

The risk of RCC development is associated with increased duration and severity of elevated blood pressure. Patients with diastolic blood pressure greater than 90 mm Hg had a 56% increased risk for development of RCC as compared to those with diastolic blood pressure less than 90 mm Hg. A systolic blood pressure greater than 160 mm Hg was associated with a 54% increased risk of RCC development compared with systolic blood pressure less than 120 mm Hg.[21] The exact pathophysiologic mechanism underlying the causal relationship between hypertension and RCC has yet to be conclusively identified and validated, but it is believed to be related to hypertension-induced renal injury and lipid peroxidation.[17] The use of antihypertensive medications do not appear to be associated with RCC development.

A well-defined link between RCC development and an inherited susceptibility has also been described. Although most RCC cases are not associated with hereditary factors and are considered “sporadic,” 2% to 3% of RCC cases are secondary to inherited syndromes.[22] Hereditary RCC is most commonly the result of an autosomal dominant transmission of a pathogenic mutation from a carrier to the offspring. Initially, one carrier parent has one healthy chromosome without the pathogenic mutation and one chromosome with the mutation. When the carrier has offspring with a healthy individual with two unaffected chromosomes, the offspring will have a 50% chance of also being a carrier. These carriers with one unaffected chromosome and one chromosome with a pathogenic mutation are at a significantly higher risk of developing RCC after being exposed to additional somatic mutations. The most common examples of hereditary RCC include VHL syndrome and Birt–Hogg–Dubé syndrome.[22]

SUBTYPES AND PATHOPHYSIOLOGY

RCC arises from the epithelium lining the renal tubules, and at least 85% of all malignancies arising in the kidney and renal pelvis can be classified as RCC.[23] The renal pelvis is less commonly affected, and only about 12% of the diagnosed kidney cancer cases each year are confirmed cancers of the renal pelvis. Other rare malignancies, affecting other parts of the kidney (eg, medullary and collecting duct carcinomas), make up the remaining 3%. The subtypes of RCC include clear cell, papillary (also known as chromophilic), chromophobe, and oncocye. Each subtype has a unique genetic pathophysiology that results in a different clinical course and response to therapy.[23]

Clear Cell Subtype: The Role of the VHL Gene

The most common histological subtype of RCC is clear cell RCC (about 80% of all RCC cases).[23,24] Clear cell RCC typically affects the proximal tubule of the kidney and is more likely to metastasize than other subtypes. An association between tumors with clear cell histology and losses in the short arm of chromosome 3 eventually led to the discovery of the gene responsible for this histologic subtype. Subsequently, *VHL* was mapped to 3p24-25.[25,26] Inactivation of the *VHL* tumor suppressor gene is now recognized as the hallmark of clear cell RCC. The Knudson and Strong two-hit model explains that the sequential inactivation of both copies of *VHL* can lead to the development of clear cell RCC.[27] In patients with sporadic disease, the two copies of *VHL* present in a healthy kidney can be inactivated via loss of chromosome 3p, epigenetic gene silencing (eg, hypermethylation of the *VHL* promoter), and genetic mutations (eg, missense mutations, nonsense mutations, or premature gene truncations). Additional mutations can result in a single, unilateral tumor. In patients with hereditary disease, one copy of *VHL* has already suffered a loss of function due to inherited germline mutations.

Thus, fewer sporadic events are then required for the inactivation of the remaining *VHL* copy. This at least partially explains why patients with hereditary disease are more likely to present with multicentric, bilateral tumors.[22,23]

3 *VHL* codes for the VHL protein (pVHL), which is expressed ubiquitously throughout the body, and is part of the complex that selects substances for ubiquitination and subsequent proteasomal degradation.[28] Because of this role, pVHL regulates cellular response to oxygen. Under normoxic conditions, hypoxia-inducible factor (HIF)-1α and HIF-2α are marked for ubiquination. Hydroxylated HIF-1α and HIF-2α bind to pVHL and are then degraded by the proteasome (see Fig. e161-1). However, when the cellular environment is hypoxic, HIF-1α and HIF-2α are not hydroxylated and do not bind to pVHL. The unbound HIF-1α and HIF-2α can then initiate transcription of hypoxia-inducible genes in the cell nucleus, which enables the cell to adapt and survive a hypoxic insult (see Fig. e161-2).[23,28] In the case of clear cell RCC, when *VHL* is mutated or silenced, pVHL is unable to bind and target HIF-1α and HIF-2α for degradation, regardless of the oxygen present in the environment. As a result, HIF-1α and HIF-2α levels increase, and they are then able to initiate transcription of pro-angiogenic and pro-mitogenic genes, including *VEGF*, *PDGF*, *TGF*, as well as genes that encode glucose transporters, and erythropoietin (see Fig. e161-3).[23,28] Eight of the ten targeted agents approved by the US Food and Drug Administration (FDA) for the treatment of RCC target these genes, and are discussed later in the chapter.

FIGURE e161-1

The role of pVHL and HIF: normal oxygen, normal *VHL*. In a normal oxygen environment, HIF is hydroxylated (OH). This enables binding of the VHL protein and subsequent attachment of a polyubiquitin chain, which is a process called ubiquitination (Ub). This allows the ubiquitin-tagged HIF to be recognized for destruction by the proteasome. The proteasome acts as a garbage disposal for compounds labeled by the ubiquitination process. An illustration shows that HIF and VHL, each bonded to OH, is attached to ubiquitin ligase, in which the HIF is bonded to a chain of four Ub. This leads to the HIF, consisting of two OH and a chain of four Ub, attaching itself to proteasome.

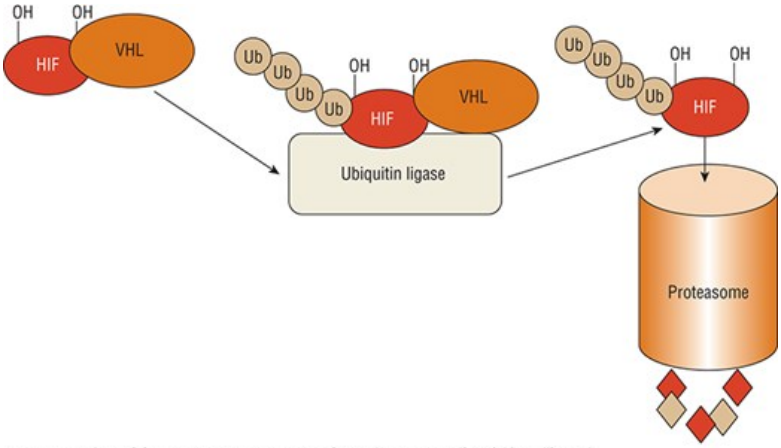


FIGURE e161-2

The role of *VHL* and HIF-1α and HIF-2α: low oxygen, normal *VHL*. In a low oxygen environment, the cell wants to increase production of substances to promote a switch to anaerobic metabolism, including enzymes involved in glycolysis and glycerol metabolism. In the situation depicted in this figure, HIF-1α is not hydroxylated and cannot bind to VHL. HIF-1α is then able to translocate into the nucleus of the cell. In the nucleus, HIF-1α combines with the HIF-β subunit and the p300 transcriptional cofactor on the hypoxia response element (HRE) that promotes the transcription of HIF-1α target genes. More than 100 genes can be activated by this complex, and include *VEGF*, *PDGF*, transforming growth factor (*TGF*), erythropoietin (*EPO*), and glucose transporter 1 (*GLUT1*). An illustration shows that when VHL inhibits HIF-1 alpha, it enters the cell nucleus, and attaches itself to HIF-beta, p300, and HRE. These undergo transcription, resulting in the release of HIF target genes, such as VEGF, PDGF, TGF, EPO, and GLUT1.

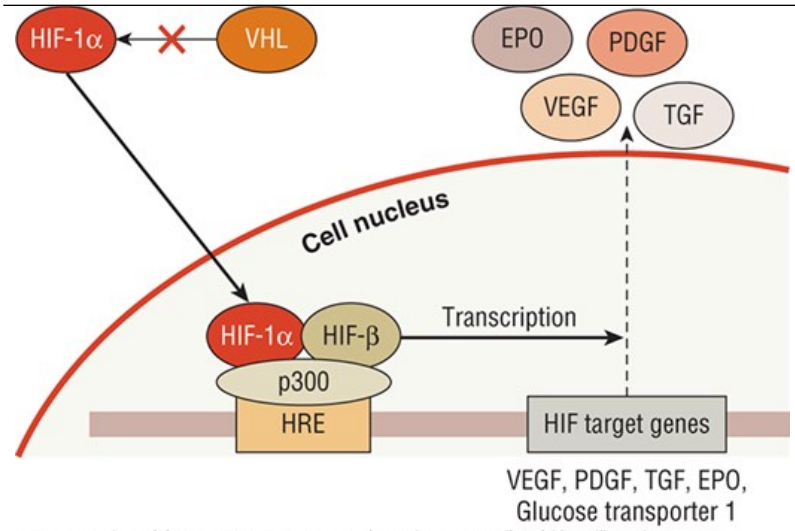
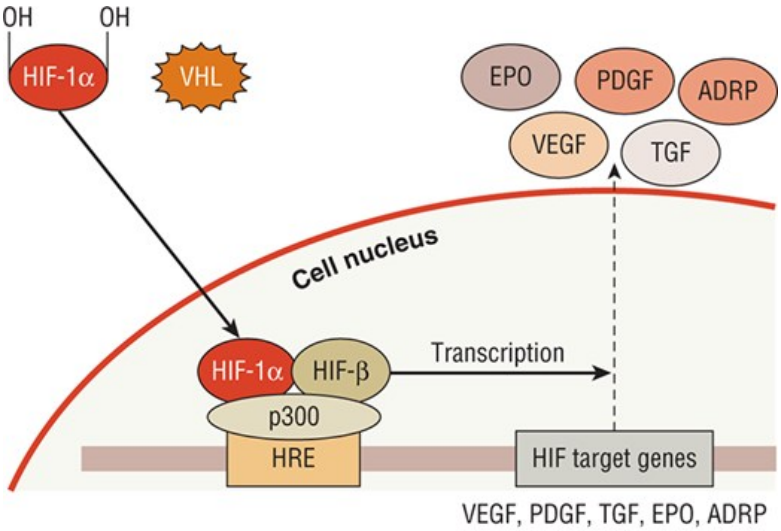


FIGURE e161-3

The role of *VHL* and HIF-1α: normal oxygen, mutated *VHL*. When the *VHL* gene is mutated, it encodes a protein that is not able to bind to the hydroxylated HIF-1α, regardless of the presence of oxygen in the environment. Because HIF-1α is not bound to VHL, it is not destroyed by the proteasome, and therefore is free to translocate into the nucleus, combine with the HIF-β subunit and the p300 transcriptional cofactor on the HRE, and initiate gene transcription. Because a hypoxic situation is not present, transcription of genes involved in angiogenesis, cellular survival, and glucose metabolism can result in an oncogenic process. (*ADRP*, adipose differentiation-related protein [responsible for neutral lipid accumulation in the cell cytoplasm, resulting in the clear cell appearance]; *EPO*, erythropoietin; TGF, transforming growth factor). An illustration shows that when VHL activates HIF-1 alpha, attached with two OH groups, it enters the cell nucleus, and attaches itself to HIF-beta, p300, and HRE. These undergo transcription, resulting in the release of HIF target genes, such as VEGF, PDGF, TGF, EPO, and ADRP.



In addition to pVHL, other growth factors and cell adhesion pathways control HIF-1α and HIF-2α activity.[28] TGF is a ligand for the epidermal growth factor receptor and, upon binding, activates the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway, in addition to other protein kinase pathways. Activation of the mTOR pathway increases the production of HIF-1α *and* HIF-2α, which can drive the oncogenic processes described earlier.[28,29] The mTOR pathway is another target for RCC treatments, which are discussed later in the chapter.

Papillary Subtypes

Papillary subtypes account for 5% to 10% of RCC cases and occur in the renal proximal tubules. They are most commonly diagnosed when the disease is localized, and thus have a more favorable prognosis than the clear cell subtype. Unlike mutations in a single tumor suppressor gene that predominantly drive the development of clear cell RCC (eg, *VHL*), papillary RCC has been associated with multiple genetic abnormalities. These tumors are further subclassified into types 1 and 2. Papillary type 1 patients are more likely to have multiple, lower grade, bilateral tumors, and have a better prognosis. In contrast, patients with papillary type 2 are more likely to present with singular, higher grade, unilateral tumors, and have a poorer prognosis.[23]

More than 80% of hereditary papillary type 1 RCC cases are associated with germline activating mutations in the mesenchymal–epithelial transition (*MET*) oncogene, located at chromosome 7q31-34.[30] These mutations are responsible for about 13% of sporadic type 1 disease, but chromosome 7 duplications are in 75% of these cases, further supporting the oncogenic role of *MET*.[28] *MET* encodes the c-MET receptor, and activation of the c-MET receptor results in increased cell proliferation and motility, and decreased cellular apoptosis.[29] Stabilization of HIF-1α and HIF-2α can also play a role in the oncogenic potential of the c-MET receptor.[31]

The papillary type 2 subtype occurs in patients with hereditary leiomyomatosis, which initially presents as multiple skin and uterine leiomyomas when patients are in their 20s and 30s, and eventually results in the formation of RCC. The gene associated with papillary type 2 RCC is the fumarase hydratase (*FH*) gene, located at chromosome 1q42.3-45. *FH* is a tumor suppressor gene that encodes the FH enzyme, which is responsible for catalyzing the conversion of fumarate to malate in the Krebs cycle. *FH* is predominantly inactivated by loss-of-function mutations, which ultimately results in HIF-1α and HIF-2α stabilization and subsequent RCC tumorigenesis.[32]

Chromophore and Oncocytoma Subtypes

The chromophore and oncocytoma subtypes combined are responsible for 5% to 10% of all RCC cases and occur in the intercalated cells of the collecting system of the kidney. Both are associated with a wide variety of chromosomal deletions and translocations. Oncocytomas are relatively benign and rarely metastasize.[23] Hereditary forms of chromophore and oncocytoma RCC are associated with the Birt–Hogg–Dube syndrome, which is characterized by hair follicle fibrofolliculomas of the face and neck and lung cysts in 15% to 30% of affected individuals. The *FLCN,* or folliculin, tumor suppressor gene is located on the short arm of chromosome 17 and is responsible for encoding the protein folliculin.[19]

Sarcomatoid Dedifferentiation

Sarcomatoid RCC is not classified as a unique tumor subtype; however, it refers to a form of tumor dedifferentiation consisting of spindle shaped cells, high cellularity and cellular atypia, and sarcoma cell features/architecture.[33] Therefore, sarcomatoid features can occur across all histological subtypes and occurs in 5% to 15% of all patients with RCC. Patients with sarcomatoid RCC are more likely to present with advanced stage disease and historically have rapid tumor growth and reduced prognosis with low response rates to targeted therapies (VEGF receptor [VEGFR]-tyrosine kinase inhibitors [TKIs] and mTOR inhibitors).[33] However, immunotherapy is changing this paradigm with increased response rates observed over VEGFR-TKIs.[34]

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Renal Cell Carcinoma

Symptoms

- Flank pain
- Fatigue
- Absence of symptoms is often seen with early disease

Symptoms of Disease Progression/Metastatic Disease

- Bone pain
- Pulmonary symptoms, including shortness of breath and cough
- Types of symptoms differ depending on location of disease spread

Signs

- Weight loss
- Anemia
- Hypertension
- Fever
- Lower extremity edema
- Hematuria
- Palpable abdominal mass

Sign of Advanced Disease

- Adenopathy

Diagnostic Tests

- CBC with differential
- Serum calcium
- Serum creatinine (SCr)
- LFTs
- Alkaline phosphatase
- LDH
- Urinalysis
- Chest x-ray
- Contrast and noncontrast CT or MRI of the abdomen pelvis
- Bone scan, brain MRI, chest CT in select cases
- Core needle biopsy in select cases

DIAGNOSIS

[4] Imaging modalities, such as CT, PET, and MRI scans, are widely used in the medical workup of numerous conditions. As a result, at least 50% of new RCC diagnoses are incidental findings when patients undergo radiographic imaging for reasons unrelated to RCC. This is a sharp increase from 1970,

when only 10% of new diagnoses were incidental.[35] Few patients present with the "classic triad" of hematuria, flank pain, and a palpable abdominal mass. Incidental diagnoses, or diagnoses made in the absence of the "classic triad" signs and symptoms that were historically associated with RCC, are usually smaller in size, lower stage, and more localized than those seen in patients who present with these signs and symptoms. In addition to the "classic triad," patients commonly present with nonspecific signs and symptoms, including fatigue, weight loss, anemia, hypertension, fever, and lower extremity edema.[35] Distant metastases predominantly occur in the lung, bone, liver, adrenal gland, and brain. Adenopathy and pulmonary symptoms are indicators of metastatic spread to the mediastinum or lung parenchyma. Elevated alkaline phosphatase or bone pain may indicate bone metastases, while neurological symptoms (eg, nausea, headaches, vision changes) may indicate brain metastases.[15]

As previously discussed, RCC development can be either sporadic or hereditary. Several differences exist between the two etiologies in terms of development patterns. Sporadic RCC most often presents as a single tumor affecting one kidney in a patient who is at least 60 years of age. These lesions may or may not be cystic in histology, and a family history is usually not reported. In contrast, those with a hereditary etiology more commonly present with numerous cystic tumors that affect both kidneys. These patients are more likely to be younger than 50 years, and they may present with other primary malignancies or have a strong family history of RCC.[35]

Laboratory evaluation should include a CBC with differential, serum calcium, SCr, LFTs, alkaline phosphatase, LDH, and urinalysis. Imaging studies are also performed to further characterize the renal tumor, assess the involvement of the inferior vena cava, and determine the patient's disease stage. Additional imaging studies, such as a bone scan or brain MRI, may be pursued depending on symptoms at presentation. Core needle biopsy is used only in rare selected cases of small lesions to guide surveillance, cryosurgery, and radiofrequency ablation strategies.[15]

STAGING AND PROGNOSIS

Factors associated with poor prognosis include positive margins after surgery, evidence of metastatic spread, presence of sarcomatoid architecture, tumor subtype, tumor grade, and tumor stage, with the latter being the most powerful prognostic indicator.[36] The eighth edition of the American Joint Committee on Cancer (AJCC) staging classification considers tumor size, number of lymph nodes involved (TNM), and the presence or absence of distant metastases.[37] Subdivisions in the tumor classification further describe the structures of the kidney that have been invaded by the tumor, including the adrenal gland, Gerota's fascia (the layer of connective tissue surrounding the kidneys), and perinephric fat that lies between the fascia and renal capsule.[37] Table e161-1 summarizes the AJCC TNM staging definitions and Table e161-2 shows the TNM stage and corresponding five-year overall survival rates.

TABLE e161-1

AJCC Staging and End Results Reporting TNM Staging Definitions

Primary Tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 7 cm in greatest dimension, limited to the kidney
T1a	Tumor ≤ 4 cm in greatest dimension, limited to the kidney
T1b	Tumor > 4 cm but ≤ 7 cm in greatest dimension, limited to the kidney
T2	Tumor > 7 cm in greatest dimension, limited to the kidney
T2a	Tumor > 7 cm but ≤ 10 cm in greatest dimension, limited to the kidney
T2b	Tumor > 10 cm in greatest dimension, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor extends into the vena cava below the diaphragm
T3c	Tumor extends into vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)
Regional Lymph Nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Distant Metastasis (M)	
M0	No distant metastasis
M1	Presence of distant metastasis

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TABLE e161-2

AJCC Staging and Five-Year Overall Survival Results by Location[38]

Stage	T	N	M	Five-Year Overall Survival (%)
I	T1	N0	M0	Local: 92.6
II	T2	N0	M0	
III	T1	N1	M0	Regional: 70.4
	T2	N1	M0	
	T3	Nx	M0	
	T3	N0	M0	
	T3	N1	M0	
IV	T4	Any N	M0	Distant: 13.0
	Any T	Any N	M1	

M, metastasis; N, node; T, tumor.

Data from Howlader N, Noone AM, Krapcho M, et al. eds. SEER Cancer Statistics Review, 1975-2017, National Cancer Institute. Bethesda, MD. Available at: https://seer.cancer.gov/csr/1975_2017/, based on November 2019 SEER data submission, posted to the SEER web site, April 2020.

5 In patients with metastatic RCC (mRCC), the MSKCC Prognostic Factors Model for Survival was developed from a retrospective analysis of 670 patients with advanced RCC from 24 different trials at MSKCC between 1975 and 1996. The model identified five factors associated with poor prognosis: Karnofsky performance status, LDH, hemoglobin, corrected serum calcium, and nephrectomy status (later interchanged with duration of time from diagnosis to initial treatment). Patients with none of the poor prognostic risk factors are considered low-risk, patients with one or two factors are considered intermediate-risk, and three or more factors are poor-risk (see Table e161-3). In this analysis, 25% of patients were classified as low-risk (median overall survival of 20 months), 53% were intermediate-risk (median overall survival of 10 months), and 22% were poor-risk (median overall survival of 4 months). Three-year overall survival for the low-, intermediate-, and poor-risk groups was 31%, 7%, and 0%, respectively.[39] This model has been validated externally.[40] In an updated analysis, the IMDC prognostic model evaluated patients with mRCC treated with VEGF pathway-targeting agents. The IMDC prognostic model confirmed the importance of hemoglobin, corrected serum calcium, Karnofsky performance status, and time from diagnosis to treatment as prognostic factors for overall survival. Elevated neutrophil and platelet counts were also independent survival prognostic factors. Of the 586 evaluable patients treated with targeted agents (sunitinib, sorafenib, or bevacizumab), 23% were favorable-risk (overall survival that was not reached after a median follow-up of 24.5 months), 51% were intermediate-risk (median overall survival of 27 months), and 26% were poor-risk (median overall survival of 8.8 months). Corresponding two-year overall survival rates for the favorable-, intermediate-, and poor-risk groups were 75%, 53%, and 7%, respectively.[41] The IMDC model has subsequently been externally validated.[42]

TABLE e161-3

Prognostic Risk Scoring Tools

MSKCC Poor Prognostic Tool	
• KPS <80% • Low serum hemoglobin (<13 g/dL [130 g/L; 8.07 mmol/L] for men and <11.5 g/dL [115 g/L; 7.14 mmol/L] for women) • Elevated corrected calcium (>10 mg/dL [2.50 mmol/L]) • Elevated serum LDH (≥300 U/L [5.00 μkat/L] or 1.5 × ULN) • Absence of prior nephrectomy (a function of duration of time between diagnosis and start of therapy, with <1 year delay being considered a poor prognostic factor)	Low-Risk: 0 prognostic factors Intermediate-Risk: 1-2 prognostic factors Poor-Risk: 3 or more prognostic factors
IMDC Criteria	
• <1 year from the time of diagnosis to systemic therapy • KPS <80% • Hemoglobin < LLN • Calcium > ULN • Absolute neutrophil count > ULN • Platelet count > ULN	Favorable-Risk: 0 prognostic factors Intermediate-Risk: 1-2 prognostic factors Poor-Risk: 3 or more prognostic factors
KPS, Karnofsky performance status; LLN, lower limit of normal; ULN, upper limit of normal	

The MSKCC and IMDC criteria are used in practice to personalize therapy for patients and have been incorporated into the National Comprehensive Cancer Network (NCCN) guidelines. For example, axitinib plus pembrolizumab, cabozantinib plus nivolumab, ipilimumab plus nivolumab, lenvatinib plus pembrolizumab, and cabozantinib alone are first-line treatment options recommended for patients with intermediate or poor-risk disease (ie, based on prognostic risk scoring tools).[15] Further, the criteria are used to determine eligibility or stratification for clinical trials.

TREATMENT

Surgical excision of the renal tumor remains the primary method of local disease control, and is performed in patients with stage I, II, or III disease.[15] In patients with advanced or metastatic disease, first-line treatment options for patients with favorable prognostic risk include combination TKIs plus immune checkpoint inhibitors, combination immune checkpoint inhibitors, and single-agent TKIs (Fig. e161-4). First-line treatment options for patients with intermediate- or poor-risk disease include combination TKIs plus immune checkpoint inhibitors, combination immune checkpoint inhibitors, single-agent TKIs, and an mTOR inhibitor (temsirolimus, poor-risk only). Subsequent-line treatment options include combination TKI + mTOR inhibitor, single-agent TKIs, combination TKIs + immune checkpoint inhibitors, combination immune checkpoint inhibitors, single-agent mTOR inhibitors, or VEGFA inhibitor. In select patients with normal organ function and excellent performance status, high-dose interleukin-2 may be considered in the first or subsequent-line settings.

Desired Outcomes

The goal of therapy for RCC depends on the stage of disease at diagnosis and other patient-specific factors, which include age, performance status, and comorbidities. In patients with localized disease confined to the kidney (stages I, II, and III), the initial treatment recommendation is surgical removal with curative intent. In patients with initially localized disease who undergo nephrectomy, 20% to 30% will relapse, with most relapses occurring in the first two years after surgery. When patients have metastatic disease, the goal of therapy is to control disease burden and prolong survival while maximizing quality of life. Even among patients with mRCC, survival outcomes depend on patient-specific prognostic factors and treatment selected based on prognostic risk.[41] The selection of each line of therapy, and even considering agents with differing mechanisms of action

within the same line of therapy, should be weighed against the risks and benefits for each individual patient.

Optimizing quality of life is always a treatment goal for all treatment modalities. Symptoms differ based on disease stage, sites of distant disease, and treatment. Patients with bone involvement may experience pain in the areas of metastatic disease that can be addressed with the use of bone modifying agents (eg, bisphosphonates or denosumab), palliative radiation therapy, and optimized daily pain medication regimens. Adherence to orally administered targeted therapies should be emphasized, both in terms of taking the medication regularly as prescribed, but also following administration directions (eg, taking the targeted therapy with or without food, and avoiding interacting medications). Adverse drug reactions should also be aggressively addressed to optimize the benefits of therapy. Hypertension, skin-related effects, and diarrhea are common adverse drug reactions of the TKIs that target the three VEGFRs, while hypercholesterolemia and hyperglycemia are common adverse drug reactions associated with mTOR inhibitors. Adverse drug reactions can be prevented or mitigated with close monitoring and/or appropriate therapeutic interventions to improve tolerability, improve medication adherence, and optimize patient quality of life. The subjective nature of many of these adverse drug reactions and disease-related toxicities can make consistent assessment challenging, but clinical trials incorporating quality-of-life outcomes, based on validated patient-reported assessments, will improve both survival and quality of life for RCC patients.

Surgery

6 Surgery represents a viable treatment modality for many RCC patients regardless of stage. Surgical options include total excision of the entire kidney (radical nephrectomy) and nephron-sparing surgery. The type of surgery performed depends on numerous patient-specific factors, which include the size and location of the renal tumor, whether multiple tumors are present, and whether the patient has unilateral versus bilateral kidney tumors. Radical nephrectomy involves excision of the entire kidney, Gerota's fascia, and ipsilateral adrenal gland after ligation of the renal vein and artery. Radical nephrectomy is preferred for patients with large, central tumors (greater than 7 cm).[43] Regardless of the functional capacity of the remaining kidney, radical nephrectomy has been associated with a higher risk for patients developing chronic kidney disease, which explains why nephron-sparing techniques have become increasingly preferred in patients with T1 disease.[44]

The most common nephron-sparing procedure is partial nephrectomy, which, in appropriately selected patients, have equivalent outcomes as those seen in patients who received a radical nephrectomy.[45] Partial nephrectomy candidates are those with smaller lesions (usually less than 4 cm) that are located in the cortical region of the kidney. Patients with bilateral tumors and those with already compromised renal function are also candidates for partial nephrectomy. Nephron-sparing surgery can also be used to describe probe-based thermal ablation procedures such as radiofrequency ablation and cryoablation. These less invasive techniques appear to have similar rates of distant recurrence to partial nephrectomy, but numerous reports suggest higher rates of local recurrences.[46] Because radiofrequency ablation and cryoablation can result in localized fibrotic reactions, surgical salvage after relapse can be compromised, and these procedures are typically reserved for patients who are not surgical candidates but still desire aggressive localized therapy. In addition to surgical excision of the tumor, some surgeons recommend extended lymphadenectomy. The procedure is controversial when lymph node involvement is not apparent, but advocates of the procedure suggest that it can be prognostic because the discovery of positive nodal involvement on lymphadenectomy can predict the presence of distant metastatic disease (even after lymph nodes have been removed).[15,16] Nearly one-third of patients relapse after surgery, but clinical trials of adjuvant treatment with radiation, immunotherapy, and numerous targeted agents failed to improve relapse-free survival in patients who initially present with localized disease (stages I-III). As a result, most patients are managed with active surveillance after local treatment, with imaging of the chest and abdomen every 4 to 6 months after surgery and then as clinically indicated. This paradigm may be changing based on the results of the S-TRAC trial, which evaluated the use of adjuvant sunitinib in patients at high risk for disease recurrence after radical nephrectomy (stages III-IV). Patients who received sunitinib had a longer median disease-free survival as compared to those who received placebo (6.8 vs 5.6 year), but also experienced increased treatment-related adverse drug reactions and lower health-related quality of life scores. Overall survival data for the trial has not yet been reported, and the optimal patient population in which to give adjuvant sunitinib, especially considering the increased risk for treatment-related adverse drug reactions, remains controversial.[15,47]

Surgery is still used for patients with metastatic disease (stage IV) and may consist of surgical resection of the renal tumor, metastectomy (surgical removal of metastatic sites), or both. Ideal candidates are those who have minimal regional lymphadenopathy, and a solitary site of metastatic disease. Metastatic sites amenable to resection include the lung, bone, brain, and soft tissue.[15,48] Clinical trials in patients with mRCC who received interferon alpha had an overall survival benefit when patients were randomized to receive a cytoreductive nephrectomy followed by interferon alpha versus systemic treatment alone. Patients with mRCC involving only the lung, with favorable prognostic features, and with a performance status of 0 or 1 appear to benefit the most from nephrectomy followed by interferon alpha.[49] The exact mechanism for the apparent improvement in overall survival is

unknown, but it has been hypothesized that nephrectomy may reduce total tumor burden, increase the time for the tumor to develop, and/or eliminate the primary source of immunosuppressive cytokines and tumor-producing growth factors. However, as response rates to systemic treatments improve, the role of surgery in mRCC is being challenged. In the CARMENA trial, intermediate- and poor-risk patients with mRCC who were treated with cytoreductive nephrectomy followed by sunitinib had noninferior overall survival rates, as compared to those treated with sunitinib alone, which contradicts the overall survival benefit seen with surgery in patients treated with interferon alpha.[50] These conflicting results suggest a patient-specific approach that balances prognostic factors, disease burden, choice of systemic treatment, and patient preferences when recommending cytoreductive nephrectomy in mRCC. Regardless of systemic treatment for mRCC, palliative nephrectomy may be an option for patients with symptoms (eg, hematuria) related to their primary tumor when removal can provide symptom relief.

Chemotherapy

Traditional cytotoxic therapy has minimal activity in the treatment of RCC. Numerous agents have been investigated, the most active being gemcitabine, vinblastine, and 5-fluorouracil. However, response rates of more than 4% to 6% were rarely observed with single agents.[23] Intrinsic resistance to chemotherapy may be partially explained by increased expression of the multidrug resistance gene 1 (*MDR1*), which encodes the P-glycoprotein (Pgp) transmembrane pump involved in drug efflux. Variable *MDR1* expression levels are observed among many normal human tissues and different tumor types, but normal kidney tissue and various RCC subtypes both express high *MDR1* levels.[51] RCC tumors with high levels of Pgp protein expression are resistant to several traditional cytotoxic chemotherapeutics. Overexpression of other drug transporter proteins, including other multidrug resistance-associated proteins, may also play a role in primary drug resistance and also in the development of secondary drug resistance. Alterations in glutathione metabolism and proteins involved with regulation of apoptosis are also possible reasons underlying resistance to traditional cytotoxic chemotherapy.[52]

Immunotherapy

7 Patients with RCC occasionally experience spontaneous regression of their disease, which has led researchers to hypothesize that RCC evokes a host immune response, which provides rationale for studying immunotherapy in RCC.[53] Interferon alpha and high-dose interleukin-2 were the standard of care for patients with mRCC prior to the targeted therapy era. Low response rates, few durable responses, and high rates of severe adverse drug reactions have limited their clinical utility over the past decade. Immune checkpoint inhibitors, including the programmed cell death protein-1 (PD-1) inhibitors such as avelumab, nivolumab, and pembrolizumab, and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) inhibitors such as ipilimumab, have improved responses as compared to these earlier efforts to harness the immune system, and are now utilized in the frontline setting for mRCC and in combination with TKIs.

Interleukin-2 is a glycoprotein primarily produced by helper T lymphocytes that stimulate the growth of cytotoxic T lymphocytes. It has been associated with response rates of approximately 20%.[54] Although the complete response rate is ≤ 10%, complete and durable responses can be achieved.[54] The FDA-approved dose of interleukin-2 is 600,000 international units/kg IV over 15 minutes given every 8 hours for a maximum of 14 doses. After this initial treatment, the dose schedule is repeated nine days later for an additional 14 doses as tolerated. Because of significant interleukin-2–related adverse drug reactions, treatment delays and discontinuations are common. The most common reported adverse drug reactions include hypotension, diarrhea, chills, vomiting, dyspnea, and peripheral edema in addition to increases in bilirubin, SCr and electrolyte abnormalities.[55] Many of these effects are related to capillary leak syndrome. Inpatient administration, intensive monitoring and supportive care are required, and many institutions administer interleukin-2 in an intensive care setting. Many patients are not candidates for interleukin-2 therapy because of their age (older than 60 years), comorbidities, compromised organ function, and poor performance status. According to the NCCN guidelines, high-dose interleukin-2 is useful in certain circumstances in the first-line and second-line treatment setting for mRCC. In both scenarios, high-dose interleukin-2 should be reserved for patients with excellent performance status and no evidence of organ dysfunction.[15]

PD-1 is a receptor expressed on activated T-cells, while its ligand, PD-L1, is expressed on immune and tumor cells. When PD-L1 binds to PD-1, the activity of T-cells is downregulated. By blocking this interaction, either at the level of PD-L1 or the PD-1 receptor, these inhibitors allow T-cells to remain activated. Because this interaction occurs in the lymph nodes and at the tumor after antigen presentation, serious adverse drug reactions (eg, autoimmune adverse drug reactions that can occur throughout the body) are limited and more manageable.[56]

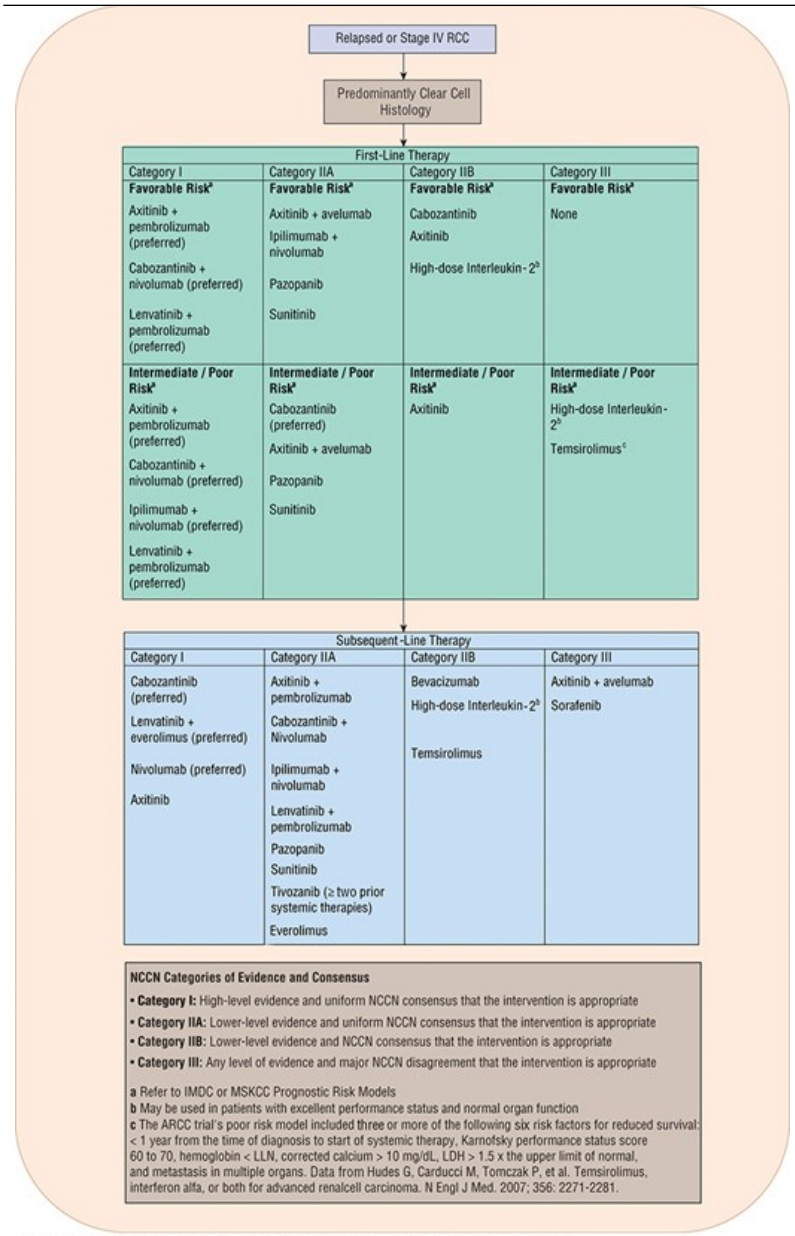
CTLA-4 receptor expression is upregulated when a cytotoxic T-cell is activated by an antigen-presenting cell. Repressive CTLA-4 receptors compete with

co-stimulatory receptors (such as cluster of differentiation 28, or CD28) on the T-cell surface to bind co-stimulatory proteins (such as B7) expressed on the antigen-presenting cell. Binding of CTLA-4 to co-stimulatory receptors leads to repression, rather than activation of T-cells. Ipilimumab binds to CTLA-4, thus preventing down-regulation of T-cells at the step of antigen presentation. Because CTLA-4 inhibitors act on T-cells during activation, the frequency and severity of autoimmune adverse drug reactions from these agents are higher than with the PD-1 inhibitors.[56]

Ipilimumab (CTLA-4 inhibitor), in combination with nivolumab (PD-1 inhibitor), is a frontline treatment option for mRCC.[57] Ipilimumab 1 mg/kg plus nivolumab 3 mg/kg intravenously every 3 weeks for four cycles, followed by maintenance with nivolumab monotherapy at a dose of 3 mg/kg intravenously every 2 weeks until disease progression or intolerable adverse drug reaction is the FDA approved dosing regimen. The objective response rate is 42%, with 9% of patients achieving a complete response. In patients with intermediate- or poor-risk disease based on IDMC scores, the 18-month overall survival rate is 75%. Rates of discontinuation due to treatment-related adverse drug reactions are high (22%), which can influence patient selection for this regimen.[57] Additionally patients with intermediate- or poor-risk disease based on IDMC have improved efficacy outcomes compared to those with favorable risk disease. The FDA approved the combination of ipilimumab and nivolumab for frontline treatment of mRCC in April 2018. Current NCCN guidelines list ipilimumab plus nivolumab as a preferred first-line regimen in patients with intermediate- and poor-risk disease (see Fig. e161-4).[15]

FIGURE e161-4

Systemic treatment options for mRCC first- and second-line therapy recommendations for relapsed or stage IV and surgically unresectable RCC. (IL, interleukin; PS, performance status RANKL, receptor activator of nuclear factor-κB ligand; RCC, renal cell carcinoma; XRT, radiation therapy.) *(Data from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Kidney Cancer: NCCN Evidence Blocks™. Version 4.2022, December 21, 2021. (NCCN) National Comprehensive Cancer Network®.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Nivolumab is the only PD-1 inhibitor approved by the FDA as monotherapy for the treatment of mRCC. The median overall survival in mRCC patients treated with nivolumab who had previously received one or two prior antiangiogenic therapies is 25 months. The objective response rate with nivolumab in this setting is 25%. Grade 3 or 4 adverse drug reactions occur in 19% of patients treated with nivolumab. The most common nivolumab treatment-related adverse drug reactions of any grade are fatigue, nausea, pruritus, diarrhea, decreased appetite and rash.[58] Single-agent nivolumab is recommended by NCCN as a second-line treatment option for clear cell, and a first-line option for patients with mRCC non-clear cell histology (see Fig. e161-4).[15]

With the single agent success of immunotherapy and the favorable adverse drug reaction profile, immunotherapy combined with TKIs offer improved clinical response rates and overall survival benefits in the first-line setting for mRCC. Four TKI + immunotherapy regimens are recommended in the first-line mRCC setting: axitinib plus pembrolizumab (PD-1),[59] axitinib plus avelumab (PD-L1),[60] cabozantinib plus nivolumab (PD-1),[61] and lenvatinib plus pembrolizumab.[62]

Axitinib can be combined with either pembrolizumab or avelumab for the first-line treatment of mRCC.[59,60] Axitinib plus pembrolizumab has a median

progression-free survival of 15 months, an objective response rate of 60%, and an improvement in overall survival over single agent TKI in the first-line setting. The benefit of this combination treatment is observed across the three IMDC risk groups and regardless of PD-L1 expression. Grade 3 or higher treatment-related adverse drug reactions occurred in 63% of the patients and 20% required a dose reduction to axitinib.[59]

Axitinib plus avelumab has resulted in a median progression-free survival of 13.3 months and an objective response rate of 53%.[60] However overall survival results are immature and currently limiting adoption of this regimen in the first-line setting. PD-L1 expression levels do not impact progression-free survival or objective response rates. Grade 3 or higher treatment-related adverse drug reactions occurred in 57% of the patients treated with avelumab plus axitinib group and 42% of patients required a dose reduction to axitinib.[60] Based on these data, the combination of pembrolizumab plus axitinib received FDA approval in April 2019 for first-line treatment of advanced RCC, and the combination of avelumab plus axitinib received FDA approval in May 2019 for first-line treatment of advanced RCC. As a result, pembrolizumab plus axitinib is preferred first-line treatment regimen by NCCN for metastatic clear cell RCC patients across risk categories, as well as a second-line treatment option for all patients with clear cell mRCC (see Fig. e161-4).[15] Avelumab plus axitinib is recommended by NCCN as a first-line option for mRCC with clear cell histology across risk categories.[15]

The combination of nivolumab plus cabozantinib is an additional treatment option in the first-line setting.[61] This combination resulted in a median progression free-survival of 16.6 months, overall survival was significantly improved compared a single agent TKI (sunitinib), and the objective response rate was 56%. Grade 3 or higher treatment related adverse events occurred in 61% of patients with 56% of patients requiring a dose reduction to cabozantinib.[61] In January 2021, the FDA approved the combination of cabozantinib and nivolumab as first-line treatment for patients with advanced RCC.

Lastly, the combination of lenvatinib plus pembrolizumab has resulted in not only the longest progression-free survival estimates (23.9 months) and objective response rates (71%) in the first-line setting of any TKI/immunotherapy combination but also the highest rate of grade 3 adverse drug reactions (72%) and percentage of patients requiring a dose reduction to the TKI (69%).[62] This combination improved overall survival compared to single agent TKI. The combination of lenvatinib plus pembrolizumab was FDA approved for the first-line mRCC population in August 2021. Taken together, both cabozantinib plus nivolumab and lenvatinib plus pembrolizumab are included as preferred first-line NCCN treatment options for clear cell, mRCC across risk groups.[15]

In summary, immunotherapy (PD-1, PD-L1, and CTLA-4 inhibitors) is an integral component of the management of patients with advanced mRCC either as single agents or in combination. PD-L1 expression does not have predictive value in mRCC. Individual patient characteristics, goal of therapy, and adverse event profile and expected tolerability of these immunotherapy combinations can inform treatment selection.

Targeted Therapy

[8] [9] Targeted agents are a cornerstone of first- or second-line therapy for the treatment of advanced RCC or mRCC (see Table e161-4 and Fig. e161-4).

TABLE e161-4

Comparison and Dosing of Targeted Agents for Patients with mRCC*

Targeted Agent	Dose and Administration	Special Population Dose	Drug Interactions
VEGF-TKIs			
Axitinib[8]	5 mg orally twice daily (may take with or without food) Maintenance	Hepatic impairment (Childs–Pugh class B), reduce dose by half	CYP3A4/5 inhibitors may increase exposure; reduce dose of axitinib by half if a strong CYP3A4/5 inhibitor is administered

	Dose: Increase every 2 weeks to 7 mg orally twice daily and then 10 mg orally twice daily		CYP3A4/5 inducers may decrease exposure
Cabozantinib[9]	60 mg orally daily (take on an empty stomach) 40 mg orally once daily (take on an empty stomach) in combination with nivolumab	Mild-to-moderate hepatic impairment, 40 mg orally daily Do not use in severe hepatic impairment	CYP3A4 inducers may decrease cabozantinib exposure CYP3A4 inhibitors may increase cabozantinib exposure
Lenvatinib[11]	18 mg orally daily (take with or without food) in combination with everolimus 20 mg orally daily (take with or without food) in combination with pembrolizumab	Severe renal impairment (CrCl <30 mL/min [0.5 mL/s]), 10 mg orally daily Severe hepatic impairment (Childs–Pugh Class C), 10 mg orally once daily	CYP3A4 and Pgp inducers may decrease lenvatinib exposure CYP3A4, Pgp, and BCRP inhibitors may increase lenvatinib exposure
Pazopanib[5]	800 mg orally daily (take on an empty stomach)	Moderate hepatic impairment, 200 mg orally once a day. Do not use in severe hepatic impairment	CYP3A4 inducers may decrease pazopanib exposure CYP3A4 inhibitors may increase pazopanib exposure
Sorafenib[7]	400 mg orally twice daily	No data	UGT1A1 and UGT1A9 substrates may have increased exposure when coadministered with sorafenib because of inhibition of glucuronidation CYP3A4 inducers may decrease sorafenib exposure

Sunitinib[6]	50 mg orally daily × 4 weeks; then off 2 weeks (may take with or without food)	Hemodialysis: no adjustment to starting dose; subsequent doses may be increased up to two-fold	CYP3A4 inducers may decrease sunitinib exposure CYP3A4 inhibitors may increase sunitinib exposure
Tivozanib[10]	1.34 mg orally daily	Moderate hepatic impairment (total bilirubin > 1.5-3 x upper limit of normal with any AST), 0.89 mg orally once daily for 21 days on treatment followed by 7 days off treatment for a 28-day cycle. Dose has not been established for severe hepatic impairment (total bilirubin > 3-10 x upper limit of normal with any AST)	Strong CYP3A inducers may decrease tivozanib exposure
VEGF Inhibitor Monoclonal Antibody			
Bevacizumab[3]	10 mg/kg IV every 2 weeks	No data	No known drug interactions
mTOR inhibitors			
Everolimus[4]	10 mg orally daily 5 mg orally daily in combination with lenvatinib	Hepatic impairment (Childs–Pugh class B), reduce dose to 5 mg orally daily	CYP3A4 and Pgp inhibitors may increase everolimus exposure CYP3A4 inducers may decrease everolimus exposure
Temsirolimus[2]	25 mg IV once weekly	If mild hepatic impairment, reduce dose to 15 mg IV once weekly. Do not use if bilirubin is greater than 1.5 times the ULN	CYP3A4 inhibitors may increase temsirolimus exposure CYP3A4 inducers may decrease temsirolimus exposure

BCRP, breast-cancer resistance protein; CrCl, creatinine clearance; CYP, cytochrome P450; UGT, uridine 5'-diphospho-glucuronosyltransferase; ULN, upper limit of normal; VEGFA, vascular endothelial growth factor A.

* *Data from FDA-approved package inserts. Available at:* https://www.accessdata.fda.gov/scripts/cder/daf/. *Accessed July 27, 2021.*

Sunitinib

Sunitinib is an orally administered antiangiogenic agent that inhibits multiple tyrosine kinases, including the three VEGFRs and PDGFR.[63] It is usually administered in a 6-week cycle at 50 mg given orally daily for 4 weeks followed by 2 weeks without treatment. Sunitinib efficacy in the first-line setting has been evaluated across several clinical trials. In the first-line setting, the median progression-free survival is approximately 8.3 months to 12.3 months among all risk groups and 5.6 to 8.4 months in intermediate- and poor-risk groups.[6,57,59–62,64] The median progression free survival is approximately 8.3 months when used as a subsequent-line treatment after cytokine therapy.[65] Sunitinib is associated with diarrhea, vomiting,

hypertension, hand–foot syndrome, hair discoloration, and myelosuppression. Most adverse drug reactions can be managed through supportive care and/or dose modifications. Sunitinib is recommended as an optional first-line treatment of mRCC in patients with clear cell histology and for second-line treatment of mRCC (see Fig. e161-4).[15]

Sorafenib

Sorafenib is another orally administered antiangiogenic agent that inhibits multiple tyrosine kinases, including the three VEGFRs, PDGFRβ, v-Raf murine sarcoma viral oncogene homolog 1, or Raf-1, v-Raf murine sarcoma viral oncogene homolog B, or BRAF, fms-like tyrosine kinase receptor-3, or FLT-3, fibroblast growth factor receptor-1 (FGFR1), and mast/stem cell growth factor receptor (c-KIT). Sorafenib is approved by the FDA for the second-line treatment of advanced or mRCC after progression on cytokine therapy at a dose of 400 mg orally twice daily. The median progression-free survival observed in patients treated with sorafenib was 5.5 months.[7] The median progression free survival was 4.7 months in patients treated with prior VEGF-targeted therapy.[7] Sorafenib is generally well tolerated with few grade 3 or 4 adverse drug reactions, although almost 5% of patients reported cardiac infarct or ischemic events.[7] Sorafenib is associated with diarrhea, nausea, vomiting, weight loss, fatigue, hand–foot syndrome, desquamating rash, hypertension, cardiac ischemia, and hemorrhagic events.[7] Sorafenib is recommended by NCCN as a second-line option for patients with mRCC (see Fig. e161-4).[15]

Pazopanib

Pazopanib is an orally administered multikinase inhibitor that is FDA approved for the treatment of mRCC. The starting dose for pazopanib is 800 mg orally once daily. Pazopanib inhibits multiple receptors, including the three VEGFRs, PDGFRα and, βFGFRs, c-KIT, interleukin-2 receptor inducible T-cell kinase, and leukocyte-specific protein tyrosine kinase.[66] Pazopanib was evaluated in a phase III clinical trial in both treatment-naïve and cytokine-pretreated patients with mRCC.[5] The overall study population had a median progression-free survival of 9.2 months. Treatment-naïve patients experienced a median progression-free survival of 11.1 months. Pazopanib was generally well tolerated, with few grade 3 or 4 adverse drug reactions.[5] A phase III noninferiority trial compared the efficacy of pazopanib versus sunitinib as first-line treatment in previously untreated patients with clear cell mRCC.[64] The progression-free survival with pazopanib was noninferior to sunitinib (8.4 months vs 9.5 months, respectively). Patients treated with sunitinib experienced a higher incidence of fatigue (63% vs 55%), hand–foot syndrome (50% vs 29%), and thrombocytopenia (78% vs 41%). Conversely, patients treated with pazopanib had a higher incidence of elevated LFTs (60% vs 43%). Quality-of-life measures, particularly those related to fatigue or soreness in the hands, feet, mouth, and/or throat, favored pazopanib. Investigators on this phase III trial concluded that pazopanib and sunitinib have similar efficacy in the first-line setting, but safety and quality-of-life profiles favor pazopanib.[64] A phase II trial had a progression-free survival for pazopanib of 7.5 months in the second-line setting following prior VEGF-targeted therapy.[67] Pazopanib is associated with transaminitis, myelosuppression, diarrhea, nausea, vomiting, fatigue, hypertension, hair discoloration, hemorrhagic events, thromboembolism, and hypothyroidism.[5] Pazopanib is recommended by NCCN as a first-line option for patients with mRCC clear cell and a second-line option for patients with mRCC (see Fig. e161-4).[15]

Axitinib

Axitinib is a second-generation orally administered multikinase inhibitor that is FDA approved for the treatment of advanced RCC after progression on one prior systemic therapy. The starting dose for axitinib is 5 mg orally twice daily and may be titrated at 2-week intervals to 7 mg twice daily and then 10 mg twice daily, if well tolerated. Axitinib is a second-generation, selective inhibitor of all three VEGFRs, and is 50 to 450 times more potent than first-generation VEGFR inhibitors (eg, sorafenib and sunitinib). Unlike first-generation agents, axitinib has limited activity beyond VEGFR blockade, which potentially results in reduced off-target adverse drug reactions.[68] Axitinib was compared to sorafenib in a phase III trial in patients with clear cell RCC who had progressed on prior therapy. The trial had a progression-free survival benefit in patients treated with axitinib when compared to patients treated with sorafenib (6.7 vs 4.7 months). The most common adverse drug reactions seen with axitinib were diarrhea, hypertension, fatigue, nausea, and dysphonia, and patients had notably less hand–foot syndrome and alopecia compared with those treated with sorafenib.[8] A second phase III trial was conducted to assess the benefit of axitinib as a first-line treatment. This open-label trial randomized patients to receive either axitinib or sorafenib. Progression-free survival was not significantly improved with axitinib compared with sorafenib. Despite the lack of a significant difference in progression-free survival between the two treatment arms, there was sufficient evidence of axitinib activity and an acceptable adverse drug reaction

profile in the first-line setting.[69] Based on the results from these two phase III trials, single-agent axitinib is an option for the first-line treatment of mRCC in patients with clear cell histology and as a second-line treatment option (see Fig. e161-4).[15]

Cabozantinib

Cabozantinib is FDA approved for the treatment of advanced RCC. The starting dose for cabozantinib monotherapy is 60 mg orally once daily in the tablet formulation (Cabometyx). The cabozantinib tablet formulation (Cabometyx) is not interchangeable with the cabozantinib capsule formulation (Cometriq) due to lack of bioequivalence.[70] Cabozantinib potently inhibit VEGFR2, as well as MET, FLT-3, Ret proto-oncogene (RET), and AXL receptor tyrosine kinase.[71] The phase II CABOSUN trial compared cabozantinib with sunitinib in patients with mRCC who had not received any prior systemic treatments and who had intermediate- or poor-risk disease based on the IMDC prognostic criteria. Treatment with cabozantinib was associated with a median progression-free survival of 8.2 months.[72]

The phase III METEOR trial compared oral cabozantinib with everolimus in patients with mRCC who had failed at least one previous therapy with a TKI. Cabozantinib was associated with a median progression free survival of 7.4 months.[9] Cabozantinib-related adverse drug reactions are similar to other approved VEGF-pathway inhibitors, and include fatigue, diarrhea, nausea, proteinuria, decreased appetite, palmar-plantar erythrodysesthesia and vomiting.[9] According to NCCN, cabozantinib is a first-line treatment option for patients with mRCC clear cell histology and intermediate- or poor-risk disease and for patients with mRCC clear cell histology and favorable-risk disease (see Fig. e161-4). Additionally, cabozantinib is a second-line treatment option in mRCC.[15]

Lenvatinib

Lenvatinib is another multitargeted TKI that inhibits VEGFRs, FGFRs, PDGFRα, RET, and c-KIT. Lenvatinib, in combination with everolimus, is FDA approved for the treatment of mRCC after failure of one prior anti-angiogenic therapy. The lenvatinib starting dose is 18 mg orally once daily when used in combination with everolimus. Approval was based on a phase II trial that compared the combination of lenvatinib plus everolimus to everolimus alone or lenvatinib alone. The median progression-free survival was 14.6 months for lenvatinib plus everolimus.[11] Combination lenvatinib plus everolimus is an appropriate second-line treatment option for mRCC (see Fig. e161-4).[15]

Tivozanib

Tivozanib is a multikinase inhibitor that inhibits VEGFR-1, VEGFR-2, VEGFR-3, c-KIT and PDGFR β.[73] Tivozanib is FDA approved for the treatment of relapsed or refractory advanced RCC following two or more prior systemic treatments. Tivozanib is administered at a starting dose of 1.34 mg orally once daily on days 1 through 21 of a 28-day cycle. The FDA approval was based on the results from a phase III trial (TIVO-3) evaluating tivozanib versus sorafenib in patients with advanced RCC following 2 or 3 prior systemic therapies. Median progression-free survival was 5.6 months with tivozanib.[10] Most common adverse events with tivozanib include hypertension, diarrhea, fatigue, decreased appetite, dysphonia, nausea, hypothyroidism, cough and stomatitis.[73] Tivozanib is recommended by NCCN as an option for subsequent line therapy in advanced RCC patients who have received two or more prior systemic therapies (see Fig. e161-4).[15]

Bevacizumab

Bevacizumab is a humanized monoclonal antibody that binds circulating VEGFA, and inhibits the ligand from binding to the VEGFRs.[63] Bevacizumab infusion at a dose of 10 mg/kg IV every 2 weeks was evaluated in a phase III trial in patients who received prior cytokine therapy.[3] The median progression free survival was 4.8 months. The most common adverse events observed in patients treated with bevacizumab were hypertension, epistaxis, malaise, hematuria, and asymptomatic proteinuria.[3] Bevacizumab monotherapy is also an option as second-line therapy (see Fig. e161-4).[15]

Temsirolimus

Temsirolimus is an intravenously administered mTOR inhibitor indicated for first-line treatment of patients with poor-risk mRCC. Temsirolimus is administered at a dose of 25 mg as an IV infusion once weekly. As discussed previously, mTOR is a downstream component of the PI3K/AKT pathway

that ultimately results in HIF regulation.[28,30] Temsirolimus was compared with interferon alpha or the combination of the two agents in a phase III trial of treatment-naive patients with higher risk mRCC. About 75% of patients were poor-risk and 25% of the patients were intermediate-risk. The trial was discontinued early, after the second interim analysis, based on temsirolimus benefit.[2] The median overall survival was 10.9 months in patients who received single-agent temsirolimus. Median progression-free survival for temsirolimus 5.5 months. Patients receiving temsirolimus were more likely to experience hyperlipidemia, hyperglycemia, and hypercholesterolemia, which were expected adverse drug reactions based on mTOR's role in the regulation of glucose and lipid metabolism. The results of this trial support the use of temsirolimus for first-line treatment of patients with poor-risk prognostic features.[74–76] Based on these results, temsirolimus is recommended by NCCN for first-line treatment in patients with mRCC with clear cell histology and poor-risk disease (see Fig. e161-4). It is also a second-line option in patients with mRCC.[15]

Everolimus

Everolimus is an orally administered mTOR inhibitor, which is approved by the FDA for patients with advanced RCC who had failed sorafenib or sunitinib therapy. Everolimus monotherapy is administered at a dose of 10 mg orally once daily. When everolimus is used in combination with lenvatinib, the dose is 5 mg orally once daily.[77] A phase III trial randomized patients who had failed previous sunitinib or sorafenib therapy to everolimus or placebo.[4] The trial had a median progression-free survival of 4 months in patients treated with everolimus. All medication-related adverse drug reactions occurred more frequently in the everolimus group than in the placebo group, but severe adverse drug reactions were uncommon. Elevations in glucose and lipids were seen because of everolimus's ability to inhibit mTOR.[78] The use of everolimus as monotherapy has decreased given its approval in combination with lenvatinib for the treatment of mRCC in the second line and beyond (see discussion above), but current NCCN guidelines include single-agent everolimus as an option in this setting (see Fig. e161-4).[15]

Summary of Targeted Therapies

Although sunitinib, sorafenib, pazopanib, axitinib, cabozantinib, and lenvatinib are all orally administered antiangiogenic multikinase inhibitors, these agents have different efficacy and adverse drug reaction profiles (see Tables e161-4 and e161-5).

TABLE e161-5

Drug Monitoring Recommendations for Targeted Agents Used in Metastatic RCC*

Targeted Agent	Adverse Drug Reactions	Monitoring Parameters	Comments
VEGFR TKIs			
Axitinib[8]	Diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, hand–foot syndrome, weight loss, vomiting, asthenia, constipation, hypothyroidism, stomatitis, arthralgia, proteinuria, rash, dry skin, headache, dyspepsia, cough Laboratory abnormalities: anemia, lymphopenia, thrombocytopenia, hyperkalemia, hyperglycemia, hypocalcemia, decreased bicarbonate, increased lipase, amylase, SCr, and LFTs	Blood pressure, VTE, hemorrhage, GI perforation or fistula, thyroid function, wound healing, RPLS, proteinuria, LFTs, pregnancy	Withhold axitinib at least two days prior to surgery. Do not resume axitinib for at least 2 weeks following major surgery and adequate wound healing.
Cabozantinib[9]	Diarrhea, fatigue, nausea, decreased appetite, hypertension, hand–foot syndrome, stomatitis, dysgeusia, rash, dysphonia, proteinuria,	CBC, electrolytes, LFTs, urinalysis, blood pressure, ECG, monitor for VTE or hemorrhagic	Withhold cabozantinib at least 3 weeks prior to surgery, including dental surgery. Do

	increased LFTs, hypertriglyceridemia, hyperglycemia, electrolyte abnormalities, venous thromboembolism, delayed wound healing	events	not resume cabozantinib for at least 2 weeks following major surgery and adequate wound healing. Do not administer to a patient at risk of severe hemorrhage.
Lenvatinib[11]	Diarrhea, fatigue, decreased appetite, hypertension, edema, stomatitis, nausea, vomiting, arthralgias/myalgias, hemorrhagic events, rash, proteinuria, QTc interval prolongation, delayed wound healing, thromboembolic events, hypocalcemia	Renal function, electrolytes, LFTs, urinalysis, blood pressure, ECG, monitor for VTE or hemorrhagic events	Withhold lenvatinib at least 1 week prior to surgery. Do not resume lenvatinib for at least 2 weeks following major surgery and adequate wound healing.
Pazopanib[5]	Elevated ALT, leukopenia, thrombocytopenia, diarrhea, nausea, vomiting, hypertension, hair discoloration, QTc interval prolongation, hemorrhage, thromboembolism, hypothyroidism	LFTs, electrolytes, thyroid function, urinalysis, ECG, blood pressure	Withhold pazopanib at least 1 week prior to surgery. Do not resume pazopanib for at least 2 weeks following major surgery and adequate wound healing.
Sorafenib[7]	Diarrhea, nausea, vomiting, anorexia, fatigue, hand–foot syndrome, desquamating rash, hypertension, cardiac ischemia, hemorrhagic events	Electrolytes, blood pressure, LFTs, ECG for QTc interval prolongation in patients with CHF, bradyarrhythmia, or electrolyte abnormalities	Withhold sorafenib at least 10 days prior to surgery. Do not resume sorafenib for at least 2 weeks following major surgery and adequate wound healing. Consider discontinuing therapy if clinical manifestations of cardiac ischemia or hemorrhagic event occur.
Sunitinib[6]	Leukopenia, thrombocytopenia, diarrhea, nausea, vomiting, anorexia, constipation, mucositis, hypertension, hand–foot syndrome, hair discoloration, hypothyroidism, decreased LVEF	Adrenal insufficiency, CBC with platelets, electrolytes, LFTs, thyroid function, urinalysis, blood pressure, ECG, for hemorrhagic events, for signs and symptoms of CHF or TLS	Withhold sunitinib at least 3 weeks prior to surgery. Do not resume sunitinib for at least 2 weeks following major surgery and adequate wound healing. Discontinue sunitinib if clinical manifestations of CHF occur. Delay or reduce dose if no clinical manifestations of CHF but EF <50% (0.5) and >20% (0.2) below baseline.
Tivozanib[10]	Hypertension, diarrhea, fatigue, decreased appetite, dysphonia, nausea, hypothyroidism, cough and stomatitis	Blood pressure, proteinuria, thyroid dysfunction, RPLS, monitor for cardiac failure, cardiac ischemia, arterial and venous thromboembolic events,	Withhold tivozanib 24 days prior to surgery. Do not resume tivozanib for at least 2 weeks after major surgery and adequate wound healing.

		hemorrhagic events, wound healing, pregnancy	
Monoclonal Antibody and VEGFA Inhibitor			
Bevacizumab[3]	Epistaxis, delayed wound healing, hypertension, thromboembolic events, proteinuria, GI perforation	Blood pressure, urine protein	Withhold bevacizumab for at least 28 days prior to surgery. Do not resume bevacizumab within 28 days after major surgery and adequate wound healing.
mTOR Inhibitors			
Everolimus[4]	Abdominal pain, asthenia, cough, dehydration, diarrhea, dyspnea, fatigue, infections, pneumonitis, and stomatitis Laboratory abnormalities: anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased SCr	Blood glucose, serum cholesterol, SCr, triglycerides, LFTs, electrolytes, and CBC	Withhold everolimus for at least 1 week prior to surgery. Do not resume everolimus for at least 2 weeks after major surgery and adequate wound healing. Avoid live vaccinations and close contact with those who receive live vaccines.
Temsirolimus[2]	Anorexia, asthenia, edema, hypersensitivity reactions, infections, interstitial lung disease, mucositis, nausea, rash, wound healing complications Laboratory abnormalities: anemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypophosphatemia, leukopenia, lymphopenia, thrombocytopenia, and increased LFTs or SCr	Blood glucose, serum cholesterol, SCr, triglycerides, LFTs, electrolytes, and CBC	Caution surgery and abnormal wound healing if administered within a few weeks starting treatment with temsirolimus or during temsirolimus therapy. Avoid live vaccinations and close contact with those who received live vaccines.

ALT, alanine aminotransferase; CHF, congestive heart failure; ECG, electrocardiogram; EF, ejection fraction; GI, gastrointestinal; LVEF, left ventricular ejection fraction; RPLS, reversible posterior leukoencephalopathy syndrome; SCr, serum creatinine; TLS, tumor lysis syndrome; VTE, venous thromboembolism.

**Data from FDA-approved package inserts. Available at:* https://www.accessdata.fda.gov/scripts/cder/daf/. *Accessed July 27, 2021.*

Sunitinib, pazopanib, axitinib, and cabozantinib have been reported to improve progression-free survival in both first- and second-line treatment settings, but sorafenib has improved progression-free survival only in the second-line treatment setting. Lenvatinib is only approved in combination with everolimus in patients who have failed other anti-angiogenic therapy. Tivozanib is approved in the subsequent line setting after two or more prior systemic therapies. In addition to differences in efficacy, these agents have differences in their adverse drug reaction profiles. Sunitinib and pazopanib are associated with higher rates of hypertension and hair discoloration than sorafenib or cabozantinib. Sunitinib is also associated with higher rates of hypothyroidism than sorafenib. Sorafenib is associated with higher rates of gastrointestinal adverse drug reactions and hand–foot syndrome than sunitinib and pazopanib. Sunitinib and tivozanib are administered cyclically. Sunitinib is given intermittently during a 6-week cycle (4 weeks on treatment, 2 weeks off treatment), and tivozanib is administered on a 28-day cycle (21 days on treatment, 7 days off treatment). Sorafenib, pazopanib,

cabozantinib, and lenvatinib are administered continuously.

Similar comparisons can be drawn between temsirolimus and everolimus, both of which are mTOR inhibitors, but the two drugs still have a few important differences. First, everolimus is administered orally once daily, whereas temsirolimus is administered as a once weekly intravenous infusion. Temsirolimus was studied in the first-line setting in poor-risk patients, while everolimus was studied in the second-line setting in patients who had progressed after sorafenib or sunitinib.

EVALUATION OF THERAPEUTIC OUTCOMES

The outcome of treatment in patients with RCC depends on the disease stage at the time of diagnosis. Whereas localized RCC has a five-year relative survival of about 93%, mRCC has a five-year survival of less than 14%.[13] The standard-of-care in patients with localized RCC (stage I-III) is surgical resection of the tumor, with a goal of long-term survival and cure. However, 20% to 30% of patients will relapse within three years, and 50% to 60% of these patients will have distant recurrence to the lungs. The NCCN Kidney Cancer guidelines recommend that patients undergo a medical history; physical examination; comprehensive metabolic panel (including blood urea nitrogen, SCr, calcium levels, and LFTs); and abdominal, pelvic, and chest imaging every 6 months for the first two years after surgery and annually thereafter.[15] For patients with stage IV and unresectable RCC, the goal of treatment is to control disease burden and prolong survival while maximizing quality of life.

Current treatment options depend on RCC histology, comorbidities, patient performance status, and prognosis risk group, and include enrollment in a clinical trial. The preferred first-line regimens for patients with favorable risk clear cell mRCC include axitinib plus pembrolizumab, cabozantinib plus nivolumab, and lenvatinib plus pembrolizumab.[15] The preferred first-line regimens for patients with intermediate- or poor-risk clear cell mRCC include axitinib plus pembrolizumab, cabozantinib plus nivolumab, ipilimumab plus nivolumab, lenvatinib plus pembrolizumab, and cabozantinib.[15] If a patient has disease progression on the initial treatment regimen, preferred subsequent treatment options include cabozantinib, lenvatinib plus everolimus, and nivolumab.[15] At each patient visit, adherence to orally administered targeted therapy regimens must be strongly emphasized, and treatment-related adverse drug reactions should be closely monitored. Because optimizing quality of life is an important therapeutic endpoint in mRCC, best supportive care should be given to all patients, which may include palliative radiation, metastectomy, and bisphosphonates or receptor activator of nuclear factor-κB ligand, or RANKL, inhibitors for the treatment of bone metastases.[15]

CONCLUSION

Renal cell carcinoma is the most frequent malignancy of the kidney and renal pelvis. Clear cell carcinoma is the most predominate histologic subtype characterized by inactivation of the *VHL* gene resulting in increased production of proangiogenic growth factors. Drug therapies targeting these growth factors play a critical role in the management of advanced disease. Immunotherapy is another integral component of drug treatment for mRCC either as single agents or combined with TKIs. Individual patient characteristics, goal of therapy, and expected tolerability of drug therapy informs treatment selection.

ABBREVIATIONS

AJCC	American Joint Committee on Cancer
AKT	protein kinase B
BMI	body mass index
CBC	complete blood count
c-KIT	mast/stem cell growth factor receptor (or CD117)
CT	computed tomography

CTLA-4	cytotoxic T lymphocyte-associated antigen-4
DNA	deoxyribonucleic acid
FDA	Food and Drug Administration
FH	fumarate hydratase
HR	hazard ratio
HIF	hypoxia-inducible factor
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
LDH	lactate dehydrogenase
LFT	liver function test
MDR1	multidrug resistance gene 1
MET	mesenchymal–epithelial transition
mRCC	metastatic renal cell carcinoma
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
mTOR	mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
PD-1	programmed cell death protein-1
PD-L1	programmed death-ligand 1
PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor
PET	positron emission tomography
Pgp	P-glycoprotein
PI3K	phosphatidylinositol 3-kinase
pVHL	von Hippel-Lindau protein
RCC	renal cell carcinoma
RET	Ret proto-oncogene

SCr	serum creatinine
TGF	transforming growth factor
TKI	tyrosine kinase inhibitor
TNM	tumor, lymph node, metastasis
VEGF	vascular endothelial growth factor
VEGFA	vascular endothelial growth factor A
VEGFR	vascular endothelial growth factor receptor
VHL	von Hippel-Lindau

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SELF ASSESSMENT QUESTIONS

1. Which of the following statements about the epidemiology of RCC is TRUE?

   A. RCC is more common in men than in women.

B. RCC is more common in pediatric patients and young adults compared to older adults.

C. RCC is more common in underdeveloped countries.

D. The incidence of RCC has decreased over the past three decades.

2. Which of the following is the most established risk factor for the development of renal cell carcinoma?

A. Smoking

B. Hypertension

C. Chronic kidney disease

D. Obesity

3. Which of the following statements about the subtypes of renal cell carcinoma is TRUE?

A. Clear cell carcinoma is the most common histological subtype, and the hallmark of the disease is mutations in the MET oncogene.

B. Clear cell carcinoma typically affects the proximal tubule of the kidney and is more likely to metastasize than other subtypes.

C. Papillary subtypes are further divided into types 1 and 2 and have a less favorable prognosis than clear cell subtype.

D. Oncocytoma subtypes are aggressive and commonly metastasize, as they are due to mutations in the VHL tumor suppressor gene.

4. Inactivation of the VHL protein (pVHL) is commonly seen in renal cell carcinoma. Which of the following statements accurately describes the role of inactivation of pVHL in oncogenesis?

A. pVHL is involved in the recognition of cells by the immune system, and its inactivation leads to immune evasion by the developing tumor.

B. pVHL regulates cellular response to oxygen. Its inactivation leads to the accumulation of hypoxia-inducible factors, that enable tumor cells to adapt and survive hypoxic insult.

C. pVHL regulates the cell cycle. Its inactivation leads to unchecked cell division and avoidance of apoptosis.

D. pVHL is expressed primarily in the kidneys and is essential to renal function. Inactivation leads to chronic kidney disease, and eventually the development of cancer.

5. Which of the following is most consistent with the clinical presentation of early stage renal cell carcinoma?

A. Hematuria, flank pain, and adenopathy

B. Anemia and cough

C. Urinary retention and bone pain

D. Asymptomatic (no new symptoms)

6. Which of the following patients with renal cell carcinoma who are in need of systemic therapy would you classify as intermediate risk based on the IMDC Criteria?

A. A 52-year-old man who was diagnosed two years ago has a Karnofsky performance status of 100%, calcium 8.7 mg/dL (2.18 mmol/L), and a normal CBC.

B. A 72-year-old woman who was diagnosed 6 months ago has a Karnofsky performance status of 70%, calcium 11.1 mg/dL (2.78 mmol/L), and a normal CBC.

C. A 65-year-old man who was diagnosed five years ago has a Karnofsky performance status of 90%, calcium 9.0 mg/dL (2.25 mmol/L), platelet 40,000/μL (40×10^9/L), and otherwise normal CBC.

D. A 60-year-old man who was diagnosed 6 months ago has a Karnofsky performance status of 100%, calcium 8.9 mg/dL (2.23 mmol/L), hemoglobin 11.0 g/dL (110 g/L; 6.83 mmol/L), and otherwise normal CBC.

7. For which of the following stages of renal cell carcinoma is surgery a treatment option?

A. Stage II

B. Stage III

C. Stage IV

D. All stages of the disease

8. Tivozanib is a multikinase inhibitor that is recommend for use in which of the following setting?

A. After surgical resection in early-stage RCC

B. Prior to surgical resection in early-stage RCC

C. First- or second-line treatment for advanced RCC

D. After two or more lines of systemic treatment for advanced RCC

9. Which of the following is TRUE about immune checkpoint inhibitors used in the treatment of renal cell carcinoma?

A. PD-1 inhibitors act in the T-cell priming phase in the lymph node, while CTLA-4 inhibitors act at the T-cell effector phase in the peripheral tissue.

B. PD-1 inhibitors generally have a more manageable adverse drug reaction profile compared with CTLA-4 inhibitors.

C. PD-1 inhibitors and CTLA-4 inhibitors cannot be used in combination due to intolerable adverse drug reactions.

D. CTLA-4 inhibitors alone are preferred for the treatment of RCC due to their superior activation of the immune response.

10. Which of the following oral agents used in the treatment of renal cell carcinoma is correctly matched with its mechanism of action?

A. Everolimus: selective TKI of pVHL

B. Sorafenib: selective TKI that inhibits multiple VEGFRs

C. Lenvatinib: multikinase inhibitor of VEGFR, FGFR, PDFR, RET, and c-KIT

D. Sunitinib: mTOR inhibitor

11. Hypertension, fatigue, and diarrhea are treatment-induced adverse drug reactions most likely related to which of the following pharmacotherapeutics options?

A. Nivolumab

B. Cabozantinib

C. Ipilimumab

D. Everolimus

12. Which of the following regimens would be appropriate for first-line treatment of favorable-risk clear cell metastatic renal cell carcinoma?

A. Temsirolimus

B. Ipilimumab plus nivolumab

C. Lenvatinib plus pembrolizumab

D. Interferon alpha

13. Patients with poor-risk metastatic renal cell carcinoma should be treated with which of the following regimens based on an overall survival benefit?

A. Everolimus

B. Ipilimumab plus nivolumab

C. Pazopanib

D. Interferon alpha

14. Patients with metastatic renal cell carcinoma who have progressed on first-line ipilimumab plus nivolumab should be treated with which of the following regimens based on a category 1 recommendation from the NCCN guidelines?

A. Cabozantinib

B. Nivolumab

C. Sorafenib

D. High-dose interleukin-2

15. Which of the following may be considered overlapping adverse drug reactions and be attributed to both lenvatinib and pembrolizumab?

A. Pneumonitis, diarrhea, and hypertension

B. Diarrhea, hypothyroidism, and transaminitis (increased liver function tests)

C. Palmar-plantar erythrodysesthesia (hand–foot syndrome), transaminitis (increased liver function tests), and pneumonitis

D. Diarrhea, palmar-plantar erythrodysesthesia (hand–foot syndrome), and hypertension

SELF ASSESSMENT QUESTIONS-ANSWERS

1. **A.** See section "Epidemiology." RCC is the sixth most common cancer in men and the ninth most common cancer in women. It is more common in developed countries (such as Europe and North American) and more common in older patients (median age of diagnosis is 64 years old). The incidence of RCC has increased over the past three decades, perhaps due to the increased use of imaging techniques such as CT or PET scans.

2. **A.** See section "ETIOLOGY." Smoking remains the most consistently established risk factor and is responsible for 10% to 30% of RCC diagnoses. Hypertension and obesity are risk factors for the development of RCC, but not to the extent of smoking. Chronic kidney disease has not been established as a risk factor for RCC (although it is often associated with other risk factors, such as hypertension).

3. **B.** See section "Subtypes and Pathophysiology." Clear cell carcinoma is the most common subtype of RCC but the hallmark of the disease is inactivation of the *VHL* gene (*MET* mutations are more commonly associated with the hereditary papillary subtype 1 tumors). Clear cell RCC commonly affects the proximal tubule (as does the papillary subtype) but is more likely to metastasize than the papillary subtype. Oncocytoma subtypes are most often benign, and hereditary forms are often associated with mutations in the *BHD* gene.

4. **B.** See section "Subtypes and Pathophysiology" on clear cell histology. Figures e161-1 and e161-2 show the role of inactivation of pVHL in the

development of a tumor.

5. **D.** See section "Diagnosis." Early stage RCC often presents with the patient not recognizing any new symptoms, and these tumors are often caught during routine imaging for other medical issues. The presence of adenopathy, anemia, cough, and bone pain would all be suggestive of metastatic disease, with tumors in areas other than the kidney (ie, lymph nodes, lungs, bones).

6. **D.** See Table e161-3 for the IMDC Criteria. Patients with one to two prognostic factors are considered intermediate-risk. Patient A has zero factors (low/favorable-risk), patient B has three factors (high-risk), patient C has zero factors (low-risk), and patient D has two factors (intermediate-risk).

7. **D.** See subsection "Surgery" under "Treatment." Surgery is an option in all stages of RCC, including those with metastatic disease, especially if they have a low disease burden.

8. **D.** See subsection "Targeted Therapy-Tivozanib" under "Treatment." Tivozanib is recommended by NCCN and FDA approved as an option for subsequent-line therapy in advanced RCC patients who have received two or more prior systemic therapies.

9. **B.** See subsection "Immunotherapy" under "Treatment." PD-1 inhibitors act in the T-cell effector phase in the peripheral tissue and therefore have a more manageable adverse drug reaction profile compared to CTLA-4 inhibitors. PD-1 inhibitors can be used in combination with CTLA-4 inhibitors (such is the case with ipilimumab and nivolumab), but there are no trials in RCC comparing monotherapy with a PD-1 and a CTLA-4 inhibitor.

10. **C.** See individual drug sections under section "Treatment" of the chapter. Everolimus is an mTOR inhibitor, sorafenib is a multitargeted TKI, lenvatinib is correctly matched (multitargeted TKI), and sunitinib is also a multitargeted TKI.

11. **B.** See section "Treatment." These three treatment-induced adverse drug reactions are common with all of the FDA-approved VEGF-pathway inhibitor TKIs used in the treatment of metastatic RCC.

12. **C.** See section "Treatment" and Table e161-4 and Fig. e161-4. First-line favorable risk metastatic RCC patients should be treated with a regimen combining an VEGF TKI with immunotherapy, such as lenvatinib plus pembrolizumab. Single-agent interferon alpha is no longer recommended in the NCCN guidelines, as novel immunotherapy options have improved clinical efficacy. Temsirolimus and ipilimumab + nivolumab are recommended in patients with intermediate/poor risk disease.

13. **B.** See section "Treatment" and Table e161-4 and Fig. e161-4. Ipilimumab plus nivolumab is the only regimen among the available choices to have a category 1 recommendation for the treatment of patients with poor-risk metastatic RCC.

14. **A.** See section "Treatment" and Table e161-4 and Fig. e161-4. Cabozantinib has a category 1 recommendation for poor-risk disease based on data from the CABOSUN trial. Single agent nivolumab has a category 1 recommendation, however, would not be considered an option since it is used in the first-line setting. The other options are not appropriate for patients with poor-risk metastatic RCC or have lower levels of evidence: sorafenib and high-dose interleukin-2 have a category 2B recommendation.

15. **B.** See section "Treatment." This was the only selection among the available options with adverse drug reactions that could be attributed to both lenvatinib and pembrolizumab. Diarrhea, hypothyroidism, and transaminitis can be attributed to both medications. All other choices include one or more adverse drug reactions that are specific to either lenvatinib or pembrolizumab.