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HOW TO

How to Treat Renal Cell Carcinoma

The Current Treatment Landscape and Cardiovascular Toxicities

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Renal cell carcinoma (RCC) represents the eighth most common malignancy in the United States, with an estimated 79,000 new cases of kidney and renal pelvis cancer to be diagnosed in 2022.[1] The treatment of RCC is highly contingent upon stage, with stage I to III disease representing localized RCC and stage IV being metastatic RCC (mRCC). Treatment for patients with stage I to III disease has remained relatively consistent, with candidates for surgery proceeding to either partial or radical nephrectomy.[2] Until recently, there has been a limited role for adjuvant systemic therapy in patients with stage I to III disease. This is evolving rapidly, however, as the US Food and Drug Administration (FDA) has approved the second adjuvant treatment for locoregional clear-cell RCC (ccRCC).[2] Few patients with stage IV disease are candidates for surgery (eg, those with limited sites of metastasis), and thus, the majority are managed primarily with systemic therapy. Here, we focus on the changing landscape of therapies for mRCC, with particular attention given to the cardiovascular risks (**Figure 1**).

CLASSES OF SYSTEMIC THERAPY FOR RCC

Broadly, systemic therapies for mRCC can be divided into 2 categories: targeted therapies and immune checkpoint inhibitors (ICIs). We focus our attention on patients with a clear-cell histology, which comprises approximately 80% of RCC cases; the remainder of patients with non-clear cell histologies (eg, chromophobe, collecting duct, etc.) do not possess similarly refined treatment paradigms.[3] The use of targeted therapy is predicated on the underlying biology of ccRCC, whereby several studies have reported somatic or germline alterations in the von Hippel Lindau (*VHL*) gene among 50% to 65% of patients.[4] Mutation of the *VHL* protein results in decreased ubiquitination of hypoxia inducible factor (HIF), a transcription factor for vascular endothelial growth factor (VEGF), which in turn enhances the vascular supply and facilitates cellular growth and proliferation among tumor cells. Thus, VEGF and its cognate receptor have represented critical targets for multiple FDA approved agents. The first agent approved in this category was sorafenib, a multikinase inhibitor targeting vascular endothelial growth factor receptor (VEGFR), rapidly accelerated fibrosarcoma (RAF), and other mediators of cell growth and division.[3] Subsequently, several similar agents have been approved, including sunitinib, pazopanib, and axitinib, among others. (**Figure 2**) In addition to these multikinase inhibitors, the monoclonal antibody bevacizumab (with affinity for VEGF) was approved at a similar time.[3]

Increasingly, other putative targets in RCC have been identified. Two representative agents include cabozantinib and lenvatinib, both of which block signaling via MET/AXL and fibroblast growth factor receptor (FGFR), respectively.[4] The mammalian target of rapamycin (mTOR) lies downstream from VEGFR in canonical signaling cascades, and 2 agents that block signaling through this moiety, temsirolimus and everolimus, have also been FDA approved.[3]

ICIs constitute the other broad class of available therapies for RCC. Currently approved ICIs work via 1) increased T-cell priming (via blockade of CTLA-4) or 2) activated immune response within the tumor (via blockade of programmed cell death protein 1 [PD-1] or its cognate ligand, programmed cell death protein ligand 1 [PD-L1]).[5] One CTLA-4 inhibitor

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(ipilimumab) and 3 PD-1/PD-L1 inhibitors (avelumab, pembrolizumab, and nivolumab) are currently approved for RCC.[3]

CASE

A 65-year-old man with no past medical history is involved in an automobile accident. In the emergency room, he undergoes a computed tomography (CT) scan of the abdomen to rule out active bleeding. The scan is remarkable for a 12-cm right-sided renal mass with features consistent with RCC. Further imaging, including a chest CT, reveals multiple pulmonary metastases ranging from 2 to 3 cm in size; magnetic resonance imaging of the brain and bone scan are unremarkable. A CT-guided biopsy of a representative lung lesion is performed; pathologic review indicates metastatic ccRCC.

The patient is initiated on a combination of cabozantinib with nivolumab. Cabozantinib is originally administered at 40 mg oral daily, and nivolumab at a dose of 240 mg intravenously on a biweekly basis. After 1 month of therapy, the patient is noted to have grade 1 hypertension, defined as a blood pressure of 120 to 139 mm Hg/80 to 89 mm Hg, controlled with lisinopril (20 mg oral daily), and at 2 months, the patient presents with mild palmar-plantar erythrodysesthesia (hand-foot syndrome).[6] As the latter is interfering with several activities of daily living, he undergoes a dose reduction to 20 mg of cabozantinib. Imaging is performed at 3-month intervals from onset of therapy and shows substantial improvement in the burden of pulmonary metastatic disease until, at 18 months, the patient is noted to have new liver metastases.

CHOICE OF FIRST-LINE TREATMENT FOR METASTATIC DISEASE

The current case recognizes that many cases of RCC are incidentally diagnosed. In addition, by recent estimates, approximately 17% of patients have clinical metastatic disease at time of diagnosis.[3] Two broad options exist for the treatment of mRCC in the first line setting, either 1) dual ICI therapy (with nivolumab/ipilimumab), or 2) combined targeted and ICI therapy (with axitinib/avelumab, axitinib/pembrolizumab, cabozantinib/nivolumab, lenvatinib/pembrolizumab).[7] Each of these treatment options possesses support from independent phase III trials using sunitinib as the control arm agent. Of these 5 regimens, only axitinib/avelumab did not demonstrate a survival advantage (relative to sunitinib), and therefore is infrequently used.[8] The optimal first-line regimen among the remaining 4 is the subject of vigorous debate in the RCC community. In broad terms, the combinations of targeted therapy with ICI yields higher response rates than dual ICI, although complete response rates appear to be relatively balanced among the regimens based on recently updated data.[8]

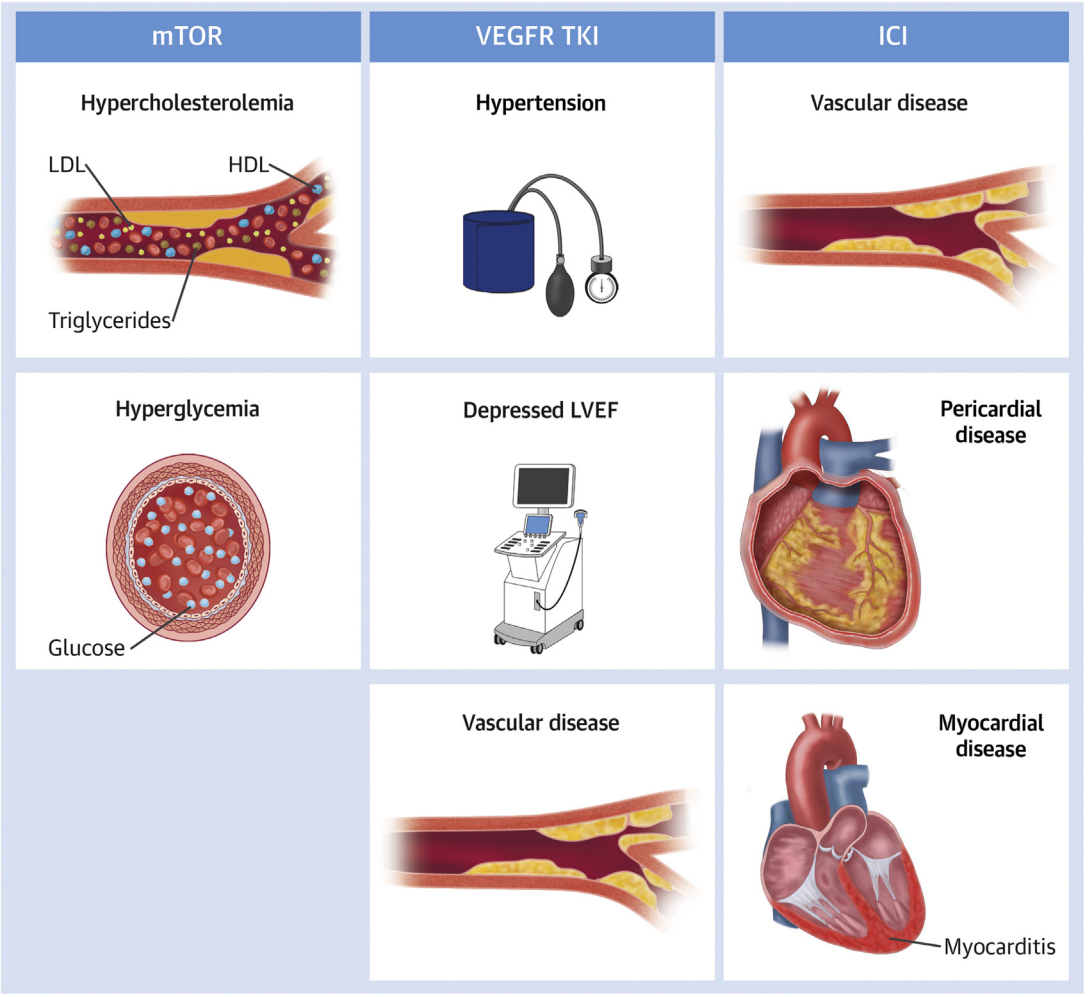
HIGHLIGHTS

- With several newly approved regimens for RCC, cardiovascular risks must be considered during treatment selection.
- Although uncommon, toxicities associated with these systemic therapies can have shortterm and long-term implications.
- Although some toxicities may be lethal, others can be managed with early intervention.
- As further agents are developed, multidisciplinary expertise is needed to manage associated cardiovascular toxicities.

Given this current state of equipoise, treatment-related toxicity has become an important factor in treatment decisions. Dual ICI therapy (as compared with monotherapy) yields higher rates of autoimmune toxicities, including colitis, hepatitis, thyroiditis, dermatitis.[9] Several of these toxicities are potentially reversible with corticosteroid therapy (eg, colitis, hepatitis), whereas others can be managed via replacement strategies (eg, levothyroxine for thyroiditis/hypothyroidism). Notably, a subset of patients with autoimmune toxicities may require more vigorous immunosuppression, for example, patients with steroid-refractory colitis may require infliximab, while patients with steroid-refractory hepatitis may require mycophenolate.[9] Autoimmune myocarditis has been the subject of many recent reports, with the incidence appearing to be relatively low (0.27% to 1.14%); despite several management strategies being proposed, this remains a highly lethal toxicity.[10]

Targeted therapies for RCC have a largely distinct toxicity profile from ICIs, although there is a possibility of overlapping toxicities (eg, colitis and hepatitis). Side effects more specific to VEGF-targeted therapies include hypertension, hand-foot syndrome, mucositis, proteinuria, and impaired wound healing.[11] Although there is no defined management of hypertension specific to VEGF inhibitors, some studies have noted benefits with angiotensin inhibitors.[12] The risk of bleeding is also salient in cardiology

FIGURE 1 **Associated Cardiovascular Toxicities of Agents Used to Treat RCC**



Toxicities associated with mTOR inhibitors **(left)**, VEGFR TKI **(middle)**, and ICI **(right)** are depicted. HDL = high-density lipoprotein; ICI = immune checkpoint inhibitor; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; RCC = renal cell carcinoma.

evaluations, requiring targeted therapies to be interrupted ahead of major surgical procedures, and carefully resumed upon wound healing.[11] It is also now well known that VEGF inhibitors may depress left ventricular ejection fraction (LVEF), although this may be less common.[13] A large, prospective study comparing sunitinib, sorafenib, and placebo in the adjuvant setting identified a rate of LVEF decline of >15% in 1.8%, 1.4%, and 0.9% of patients, respectively.

The selection of cabozantinib/nivolumab in this patient was predicated on the higher overall response rates seen with this regimen as compared with dual ICI therapy with nivolumab/ipilimumab.[8] Additionally, recent data pertaining to quality of life showed a cabozantinib/nivolumab advantage in several domains over sunitinib control.[11]

CASE (CONTINUED)

After the development of progressive liver metastases following treatment with cabozantinib/nivolumab for 18 months, the patient was counseled regarding treatment options and pursued therapy with lenvatinib and everolimus. Lenvatinib was administered at a dose of 18 mg oral daily with everolimus at 5 mg oral daily. The patient developed shortness of breath after 1 month of therapy, and a CT scan of the chest showed diffuse infiltrates bilaterally, consistent with interstitial pneumonitis. Other disease-related findings were stable. Therapy with everolimus was discontinued, and the patient was maintained on lenvatinib, but with a dose reduction to 14 mg daily, given worsening diarrhea. The patient was able to

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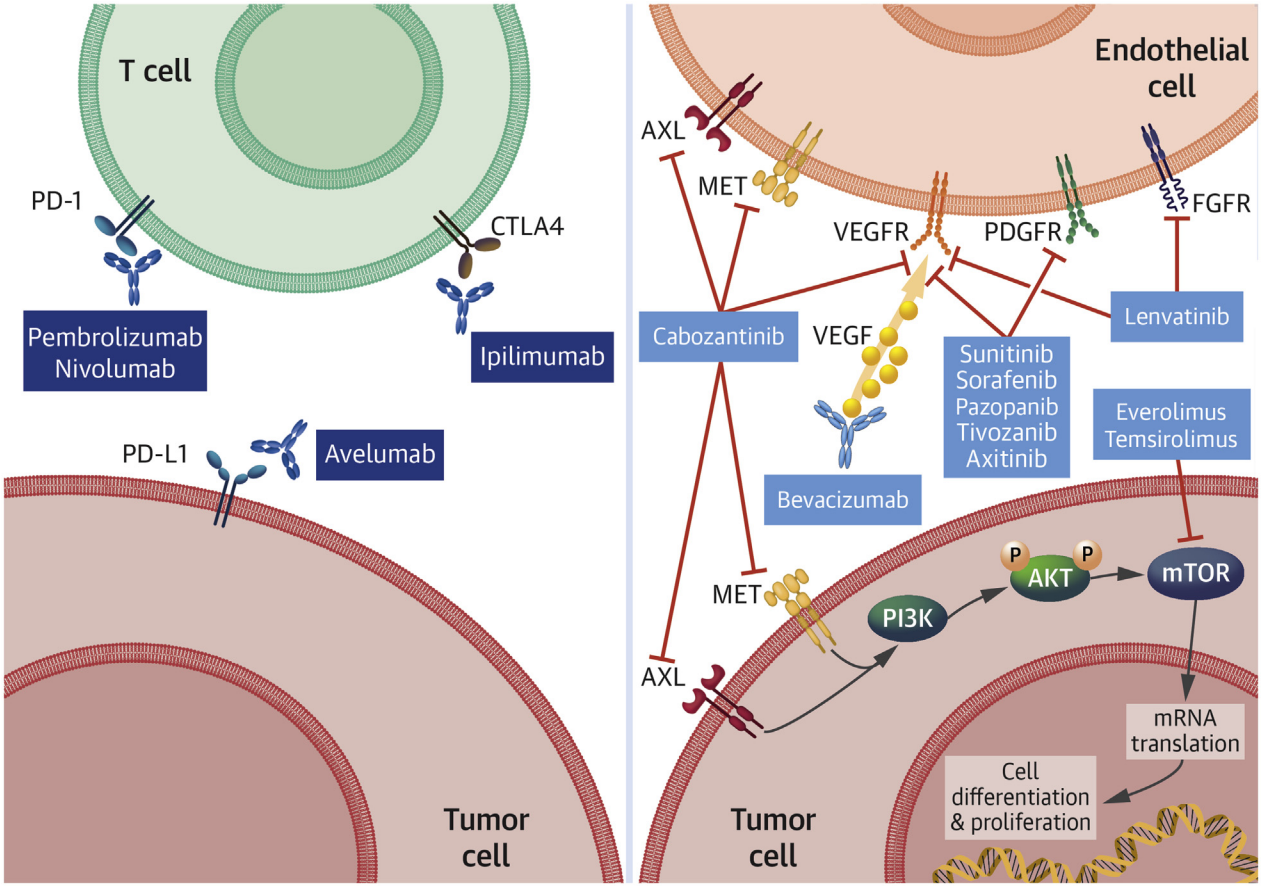
FIGURE 2 Mechanisms of Systemic Therapies Used to Treat mRCC



Major molecules involved in each pathway are depicted for immune checkpoint inhibitors **(left)** and targeted therapies **(right)**. P indicates protein phosphorylation. AKT = protein kinase B; MET = hepatocyte growth factor receptor; mRCC = metastatic renal cell carcinoma; mTOR = mammalian target of rapamycin; PDGFR = platelet-derived growth factor receptor; PI3K = phosphoinositide 3-kinase.

tolerate this dose, and imaging at 3 months showed a partial response, with a 40% reduction in disease burden within the liver. The patient continued this regimen for a total of 12 months before his disease progressed, and in the context of worsening pain-related symptoms, elected to engage hospice care and died 3 months thereafter.

CHOICE OF SECOND-LINE TREATMENT

For a patient who progresses on first-line therapy, multiple options exist. The regimen of lenvatinib with everolimus was first assessed in a randomized, phase II study, comparing this agent to lenvatinib monotherapy and everolimus monotherapy.[3] The combination demonstrated a significant improvement in progression-free survival (14.6 months vs 5.5 months with everolimus monotherapy; $P = 0.0005$), leading to FDA approval. For those patients not exposed to prior cabozantinib (as in the current case), cabozantinib would also be an appropriate choice for second-line treatment.[7] This agent has demonstrated benefit in a phase III trial comparing cabozantinib to everolimus in the second-line setting and beyond. Most recently, the agent tivozanib (a potent and specific VEGFR inhibitor) has shown benefit in a phase III trial in which the agent was compared with sorafenib, with specific attention given to the role of this agent in the third- and fourth-line settings.[14]

In the current case, the patient developed shortness of breath after initiating therapy with lenvatinib/everolimus. Although there is a possibility of a cardiac etiology (depressed LVEF with lenvatinib), patients receiving mTOR inhibitors such as everolimus are also susceptible to interstitial pneumonitis.[15] If detected early, these toxicities are potentially

reversible. mTOR inhibitors have been associated with hypertriglyceridemia and hyperglycemia, and thus, long-term use could affect cumulative cardiovascular risk.[15]

SPECIAL SETTINGS AND CONCLUSIONS

The current case outlines a prototypical patient with de novo mRCC. However, there are many different manifestations of this disease. For instance, the majority of patients with mRCC initially present with localized disease, with stage I patients appropriate for observation, whereas high-risk stage II and stage III patients may be candidates for adjuvant therapy with pembrolizumab.[2] This strategy stems from the recently published KEYNOTE-564 trial, comparing pembrolizumab to placebo in this population, with pembrolizumab associated with a significant improvement in disease-free survival.[16] Further, the current case did not address less common histological subtypes of RCC. For instance, papillary RCC represents 10% to 15% of cases—in this disease, the current standard of care is targeted therapy with the agent cabozantinib.[2,3] Among those with rarer subtypes, such as collecting duct carcinoma or renal medullary carcinoma, cytotoxic chemotherapy remains the standard treatment approach. Whereas a detailed overview of these subtypes is beyond scope for this primer, it should be noted that management may differ from that of clear cell mRCC.

Finally, several novel agents are in their final stages of development for the treatment of mRCC. For example, agents blocking HIF are actively being explored and will likely become available in the near future, whereas cellular therapies and bispecific antibodies, agents that transformed care for hematologic diseases, are also in early stages of development for mRCC. Whereas such agents may be associated with improved clinical outcomes among patients with mRCC, there will likely be new toxicity considerations, further emphasizing the need for effective multidisciplinary care of this population.

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