Treatment of Metastatic Renal Cell Carcinoma

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Abstract

Therapy for advanced renal cell carcinoma is currently predicated on inhibition of VEGF and mTOR pathways and selective use of immunotherapy. Treatment of metastatic renal cell carcinoma (mRCC) remains a very active area of research, and new strategies and agents are undergoing clinical trials. With the advent of new systemic agents, some of the principles of treatment are being reevaluated. This article provides a succinct and focused review of the landscape in the treatment of mRCC.

Key words: renal cell carcinoma, adjuvant, neoadjuvant, immunotherapy

Introduction

Over the past decade, the treatment of metastatic renal cell carcinoma (mRCC) has been an exciting field for researchers and patients alike as new treatments have made their way into clinical practice. VEGF and mTOR inhibitors have become the mainstay of treatment, replacing interferon. This field has grown quickly, and we now have multiple agents available for treating patients. This has led to more questions than we can answer, including what sequence or combination can maximize the benefit to patients. This article highlights some of the emerging trends and challenges facing today's investigators and clinicians.

The Role of Nephrectomy in the Era of Targeted Therapy

In the era of interferon therapy, 2 trials by SWOG and EORTC established an overall survival (OS) benefit for cytoreductive nephrectomy in the setting of mRCC.[1,2] Currently, 2 ongoing trials are attempting to further define the role of cytoreductive surgery in the era of targeted therapy: the CARMENA trial, which randomizes patients with mRCC to sunitinib alone versus nephrectomy followed by sunitinib (NCT00930033); and the SURTIME trial, which compares immediate nephrectomy with deferred nephrectomy after 3 cycles of sunitinib (NCT01099423). Retrospective analyses by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) suggest that even when biases for patient referral for surgery are accounted for, in the era of targeted therapy there may still exist a role for cytoreductive surgery based on an observed OS benefit.[3] It is important to note that poor-risk patients who were not expected to survive more than 12 months did not benefit from surgery.[3]

The Roles of Neoadjuvant and Adjuvant Targeted Therapy and Metastasectomy

Adjuvant cytokine-based immunotherapy trials did not demonstrate a survival benefit. The role of adjuvant targeted therapy is currently being investigated, and so far the initial reports for sorafenib and sunitinib are not promising.[4] Similarly, the role of neoadjuvant targeted therapy is being studied. Until further data are available, the use of targeted therapy (VEGF inhibitors or mTOR inhibitors) is not recommended in either setting outside of a clinical trial.

Metastasectomy is an appropriate surgical intervention for a select group of patients and is associated with improved cancer-specific survival.[5] Metastasectomy can be done at the time of nephrectomy to render the patient disease-free, either at the time of recurrence after nephrectomy or after systemic treatment for metastatic disease after nephrectomy. Generally, patients most likely to benefit are those with a good performance status and low volume and number of metastases in a single organ system, such as lung, adrenal, or bone, as well as those patients who can have complete resection.[6]

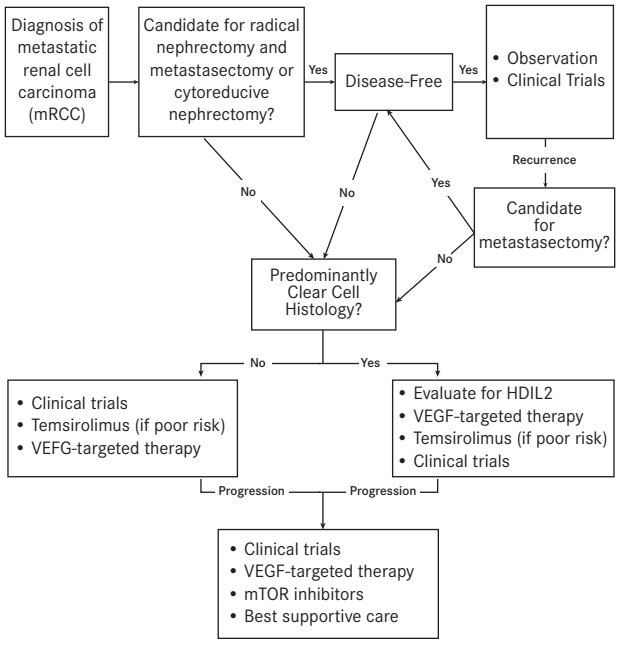
Choosing a Risk Stratification Paradigm

There are 2 widely used risk stratification models for kidney cancer: the Memorial Sloan Kettering Cancer Center (MSKCC) model[7,8] and the IMDC model, also known as the Heng Criteria.[9] The advantage of the Heng Criteria is that it was derived and validated using data from patients who had received VEGF-targeted therapy, and as a result, it may be more applicable in today's clinical practice. However, there is significant overlap between the 2 models, and most patients will be similarly risk-stratified using either criteria.

Choice of First-Line Treatment

While several targeted therapy agents have received US Food and Drug Administration (FDA) approval and are available in the first-line setting, high-dose interleukin-2 (IL-2) still has a sig-

FIGURE. Clinical Decision-Making in Metastatic Renal Cell Carcinoma.



nificant role in this setting in the treatment of mRCC. This is based on clinical trial data demonstrating durable remission in about 10% of patients,[10,11] and increasing evidence that even a minor response to IL-2 is associated with better outcomes.[12] Patient selection is important. Ideal candidates for high-dose IL-2 have good performance status, no bone metastases, relatively low-volume disease, and prior nephrectomy.[13-15] In addition to these factors, toxicities of high-dose IL-2 are significant and must be balanced against the potential benefits.[16]

It is also important to recognize that high-dose IL-2 is an inpatient therapy and is only available at centers with highly experienced staff. Therefore, high-dose IL-2 may not be a viable option for many patients. For those patients who are not candidates for or don't have access to high-dose IL-2 therapy, therapy with one of the multiple agents that target VEGF and/or mTOR is an option.

For patients with poor-risk disease, temsirolimus is a reasonable option, as is a VEGF inhibitor based on level 1 evidence from a phase III trial.[17] Of the 2 available mTOR inhibitors, everolimus does not have a proven role in first-line therapy.[18] The choice of VEGF inhibitor in this setting is less clear. Data from the COMPARZ trial[19] suggest that although sunitinib and pazopanib are equally effective, pazopanib may have an edge over sunitinib with respect to side effects and quality of life. A phase III trial of axitinib versus sorafenib in the first line did not meet its endpoint but demonstrated safety and activity, and therefore provides some support for the use of axitinib as a frontline agent.[20]

Patients with a solitary metastasis should be evaluated for metastasectomy. Symptomatic or worrisome bone lesions should be evaluated for stereotactic radiation therapy.[21] Brain metastases should be treated surgically or by stereotactic radiosurgery or whole-brain radiation therapy prior to systemic therapy.[22-24]

Choice of Second-Line Treatment

For patients who develop progressive disease after immunotherapy with IL-2, or less commonly in recent years with interferon-α (IFN-α) therapy, the same principles as first-line targeted therapy apply. For patients with disease progression on a VEGF-targeting agent, an mTOR inhibitor or another VEGF-targeting agent may be appropriate. Axitinib has the best evidence base as a second-line option,[25] with everolimus having level 1 evidence to support its use after failure of 1 or 2 VEGF-targeted agents.

Non–Clear Cell Histologies

While non–clear cell histologies constitute a minority of cases of RCC, they pose a significant therapeutic challenge. A meta-analysis of targeted therapy clinical trials suggests that VEGF-targeting agents may have activity in patients with non–clear cell or clear cell histologies with sarcomatoid features.[26] These tumors do not respond to immunotherapy with IL-2.[14] There has been modest response to chemotherapy in tumors with predominant non–clear cell histologies, including the combination of doxorubicin and gemcitabine for sarcomatoid tumors,[27] and gemcitabine plus platinum for collecting duct carcinomas.[28]

Ongoing Clinical Trials and Future Directions

Ongoing clinical trials are directed at the adjuvant setting, the role of cytoreductive nephrectomy, and novel targeted therapies and immunotherapies.[29] With the advent of active and tolerable immunotherapy in the form of vaccines and inhibitors of immune checkpoint mediators CTLA4, PD-1, and PD-L1, new treatment options are on the horizon.[30,31]

Based on some early results signaling safety and activity in mRCC, vaccines alone or in combination with other cytokines are being evaluated to define their role in the treatment of RCC.[32] Similarly, immune checkpoint agents are actively being studied in various cancer types including mRCC, with some early results showing safety and activity.[33] Larger trials are under way, and until results are available, these strategies remain experimental. The **Figure** provides a diagram of clinical decision making in mRCC, and the **Table** provides a summary of key clinical trials in this field.

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TABLE. Key Completed Phase III Clinical Trials in Metastatic Renal Cell Carcinoma

Trial	Arms	N	MSKCC Prognostic Risk: Favorable Intermediate Poor	Toxicity (all grades)[a]		OS PFS ORR (CR+PR) CR
Escudier et al[34]	Sorafenib Placebo	451 452	NR 48% vs 49% 52% vs 50%	Diarrhea Fatigue HFS HTN	43% 37% 30% 2%	19.3 vs 15.9 mo 5.5 vs 2.8 mo[b] 11% vs 2%[b] <1% vs 0%
Motzer et al[35]	Sunitinib IFN-α	375 375	38% vs 34% 56% vs 59% 6% vs 7%	Diarrhea Fatigue HFS HTN	53% 51% 20% 24%	26.4 vs 21.8 mo 11 vs 5 mo[b] 47% vs 12%[b] 0% vs 0%
Escudier et al[36]	Bevacizumab + IFN-α Placebo + IFN-α	327 322	27% vs 29% 56% vs 56% 9% vs 8%	Diarrhea Fatigue HFS HTN	20% 33% NR 26%	23.3 vs 21.3 mo 10.2 vs 5.4 mo[b] 31% vs 13%b 1% vs 2%
Rini et al[37]	Bevacizumab + IFN-α IFN-α	369 363	26% vs 26% 64% vs 64% 10% vs 10%	Diarrhea Fatigue HFS HTN	NR 93% NR 28%	18.3 vs 17.4 mo 8.5 vs 5.2 mo [b] 13% vs 9% <1% vs <1%
Sternberg et al[38]	Pazopanib Placebo	290 145	39% vs 39% 55% vs 53% 3% vs 3%	Diarrhea Fatigue HFS HTN	52% 40% <10% 40%	22.9 vs 20.5 mo 9.2 vs 4.2 mo[b] 30% vs 3%[b] <1% vs 0%
Motzer et al[39-41]	Tivozanib Sorafenib	260 257	27% vs 34% 67% vs 62% 7% vs 4%	Diarrhea Fatigue HFS HTN	22% 18% 13% 44%	28.8 vs 29.3 11.9 vs 9.1 mo[b] 33% 23% 1% vs 1%
Hutson et al[20]	Axitinib Sorafenib	192 96	49% vs 53% 44% vs 40% 4% vs 2%	Diarrhea Fatigue HFS HTN	50% 33% 26% 49%	NR 10.1 vs 6.5 mo 32% vs 15% 0% vs 0%
Rini et al[25]	Axitinib Sorafenib	361 362	28% vs 28% 37% vs 36% 33% vs 33%	Diarrhea Fatigue HFS HTN	55% 39% 27% 40%	NR 6.7 vs 4.7 mo[b] 19% vs 9%[b] 0% vs 0%
Motzer et al[42,43]	Everolimus Placebo	277 139	29% vs 28% 56% vs 57% 14% vs 15%	Fatigue Rash Stomatitis Pneumonitis	31% 29% 44% 14%	14.8 vs 14.1 mo 4.9 vs 1.9[b] 1.8% vs 0% 0% vs 0%
Hudes et al[17]	Temsirolimus IFN-α Temsirolimus + IFN-α	209 207 210	0% vs 0% vs 0% 31% vs 24% vs 24% 69% vs 76% vs 76%	Fatigue Rash Anemia Nausea	51% 47% 45% 37%	10.9 vs 7.3 vs 8.4 mo[b] 5.5 vs 3.1 vs 4.7 mo[b] 8.6 vs 4.8% vs 8.1% NR
Motzer et al[19]	Sunitinib Pazopanib	548 554	NR	Fatigue HFS Rash Mucositis	63% vs 55% 50% vs 29% 23% vs 18% 26% vs 11%	29.3 vs 28.4 mo 9.5 vs 8.4 mo 29% vs 33% 0.5% vs 0.2%

[a]Toxicity for agent in the intervention arm.
[b]Significant.

CR indicates complete response; IFN, interferon; HFS, hand-foot syndrome; HTN, hypertension; mo, months; MSKCC, Memorial Sloan-Kettering Cancer Center; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

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