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REVIEW

Renal cell carcinoma: An update for the practicing urologist

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Abstract Systemic therapy for metastatic renal cell carcinoma (mRCC) has evolved drastically, with agents targeting vascular endothelial growth factor (VEGF) and the mammalian target of rapamycin (mTOR) now representing a standard of care. The present paper is to review the current status of relevant clinical trials that were either recently completed or ongoing. (1) Though observation remains a standard of care following resection of localized disease, multiple trials are underway to assess VEGF- and mTOR-directed therapies in this setting. (2) While the preponderance of retrospective data favors cytoreductive nephrectomy in the context of targeted agents, prospective data to support this approach is still forthcoming. (3) The first-line management of mRCC may change substantially with multiple studies exploring vaccines, immune checkpoint inhibitors, and novel targeted agents currently underway. In general, prospective studies that will report within the next several years will be critical in defining the role of adjuvant therapy and cytoreductive nephrectomy. Over the same span of time, the current treatment paradigm for first-line therapy may evolve.
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1. Introduction

Systemic therapy for metastatic renal cell carcinoma (mRCC) has evolved markedly in recent years, due in large part to a better understanding of RCC biology. In 50%—75% of patients, aberrations in the von Hippel Lindau (*VHL*) gene leads to increased expression of hypoxia inducible factor-α (HIF-α) [1]. HIF-α expression in turn drives an increase in vascular endothelial growth factor (VEGF). Through downstream signaling via the mammalian target of rapamycin

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(mTOR), VEGF drives tumor growth and angiogenesis. Translating these findings from bench to bedside, there are multiple inhibitors of VEGF and mTOR that are now clinically utilized. Small molecule VEGF-tyrosine kinase inhibitors (VEGF-TKIs) that have shown clinical benefit in phase III trials include sunitinib, sorafenib, pazopanib and axitinib, and the monoclonal antibody bevacizumab (in combination with interferon-α [IFN-α]) has similarly shown benefit in a phase III trial in the front-line setting [2—5]. Two mTOR inhibitors (temsirolimus and everolimus) have also garnered FDA approval on the basis of positive phase III data [6,7].

The utilization of these agents brings up several key issues in multidisciplinary management. For instance, in other disease states (e.g., breast cancer and colorectal cancer), systemic therapies frequently transition from the metastatic to adjuvant setting. Multiple studies to evaluate VEGF-TKIs and mTOR inhibitors as adjuvant treatment are underway, but at the present time, the standard of care following nephrectomy remains observation [8]. A second multidisciplinary issue is the use of cytoreductive nephrectomy in patients with synchronous metastases. Although prospective trials have firmly established the role of this procedure in the context of immune-based therapies (e.g., IFN-α and interleukin-2 [IL-2]), it is unclear whether cytoreductive nephrectomy is essential in patients with synchronous metastases receiving targeted therapies [9]. Finally, although implementation of systemic therapy for metastatic disease typically takes place in the medical oncology clinic, the evolving healthcare landscape in multiple countries may frequently necessitate involvement of the urologist.

The current review provides a framework for approaching these multidisciplinary issues in RCC management. The status of adjuvant therapy trials is discussed, along with trials and retrospective data addressing the role of cytoreductive nephrectomy. Finally, recent innovations in therapy for mRCC are discussed — given the scope and intent of this review, discussion is largely focused on front-line management.

2. Evidence acquisition

A Medline database search was conducted from the years 2000—2014 using the following search terms: "adjuvant therapy (of) renal cell carcinoma", "cytoreductive nephrectomy", and "systemic therapy (for) metastatic renal cell carcinoma". An identical search was performed using the American Society of Clinical Oncology Abstract database. Search results were filtered to exclude review articles, editorials and letters. Prospective and retrospective studies were retained. Trials in progress or recently completed that were relevant to the current manuscript were identified through a search of Clinicaltrials.gov.

3. Evidence synthesis

3.1. Current status of adjuvant therapy for RCC

The concept of exploring systemic treatments for RCC in the adjuvant setting is not new — multiple prospective studies were completed in the immunotherapy era. Several notable examples include a study by the Eastern Cooperative Oncology Group (ECOG), in which 283 patients with pT3-4aN0M0 or pTxN1-3M0 RCC were randomized to receive IFN-α for a period of 6 months or observation [10]. Interestingly, this study showed a higher 5-year overall survival (OS) with observation as compared to IFN-α (62% vs. 51%, $p = 0.09$). An Italian study employed a similar randomization in patients with high-risk localized RCC and similarly showed no significant improvement in clinical outcome with adjuvant IFN-α [11]. IL-2 has also been assessed as an adjuvant. The Cytokine Working Group (CWG) conducted a study in which patients received 1 cycle of high-dose IL-2 or observation [12]. A futility analysis conducted after enrollment of 69 patients led to early closure after it was determined the study would not be able to achieve its primary endpoint of improving 2-year disease-free survival (DFS).

Failed attempts at proving clinical benefit with adjuvant immunotherapy have not stifled efforts to explore targeted therapies in the same setting (Table 1). The largest study to date exploring adjuvant targeted therapy is the ASSURE trial (ECOG 2805), which has completed accrual of 1943 patients [13]. Patients were randomized to receive either sunitinib, sorafenib or placebo for a duration of 1 year, with stratification by histology and ECOG performance status. Although efficacy data from this study is still forthcoming, a cardiac substudy from ASSURE has been reported [14]. Serial assessments of ejection fraction (EF) suggested no significant decline with sunitinib or sorafenib as compared to placebo. Notably, concerns for cardiac toxicity with these agents have emerged in the metastatic setting [15].

Several other studies are exploring the role of sunitinib and sorafenib in the adjuvant setting. The SORCE trial accrued a total of 1711 patients across western Europe and Australia, and randomized patients with an intermediate or high Leibovich score to either sorafenib for 3 years, sorafenib for 1 year followed by placebo for 2 years, or placebo for 3 years [16]. Although efficacy data is still forthcoming, the SORCE investigators have reported key demographic and clinicopathologic data from their trial [17]. Notably, 182 patients (10.6%) had pT1b disease, and 21% of patients had pT2 disease. Thus, although the study was intended to encompass a group of at-risk patients, a

Table 1 Completed and ongoing adjuvant trials of VEGF-TKIs and mTOR inhibitors in RCC.

Trial (sponsor)	Sponsor	Agent assessed	n	Completion (projected or actual)
ASSURE	ECOG	Sunitinib/sorafenib	1943	Sep 2010
ATLAS	Pfizer	Axitinib	592	June 2017
EVEREST	SWOG	Everolimus	1218	Oct 2021
PROTECT	GSK	Pazopanib	1500	April 2016
SORCE	MRC	Sorafenib	1420	Dec 2012
S-TRAC	Pfizer	Sunitinib	720	Nov 2015

VEGF-TKIs, vascular endothelial growth factor (VEGF)-tyrosine kinase inhibitors; mTOR, mammalian target of rapamycin; RCC, renal cell carcinoma.

substantial proportion had relatively low-risk disease. The low frequency of anticipated events in this subset could have implications in terms of the likelihood of SORCE meeting its primary endpoint (improvement in DFS). Approximately 42% of patients had an open nephrectomy, while the remainder had a laparoscopic procedure. With this roughly even divide, SORCE may also provide key insights into the impact of surgical technique on the efficacy of adjuvant therapy.

In contrast to SORCE, the S-TRAC study will randomize 720 patients with high-risk disease using the UCLA Integrated Staging System to either sunitinib or placebo for 1 year [18]. Outside of sunitinib and sorafenib, there are two studies investigating distinct VEGF-TKIs. In the PROTECT trial, a total of 1500 patients with pT2N0M0 (Fuhrman grade 3−4), pT3-4N0M0, or pTxN1M0 received either pazopanib or placebo for a total of 1 year. The ATLAS trial is an ongoing effort in which 592 patients with pT2-4N0M0 or pTxN1M0 RCC will receive axitinib or placebo over the span of 3 years.

A common thread amongst most of the adjuvant trials of VEGF-TKIs is difficulties in dosing. In the ASSURE trial, the starting doses of sunitinib and sorafenib had to be reduced from conventional doses used in the metastatic setting. If patients tolerated a lowered dose during the first two cycles of therapy, the dose was subsequently escalated. The SORCE and PROTECT studies also similarly required a reduction in the starting dose of sorafenib and pazopanib, respectively. To explain the difference in tolerability of adjuvant treatment, one might posit that patients with localized disease may have a different biology as compared to patients with metastatic disease. However, a more likely explanation is that patients receiving adjuvant therapy may have a lower threshold for accepting toxicity for the end result of lowering the rate of disease recurrence. In contrast, patients with metastatic disease may be willing to tolerate a higher level of toxicity to combat further disease progression.

Two other trials of targeted therapy in the adjuvant setting deserve mention. In the EVEREST trial, a total of 1218 patients with pT1bN0M0 (Fuhrman grade 3−4) or pT2-4N1-3M0 disease will be randomized to either everolimus or placebo for 1 year [19]. The study has completed roughly half of its anticipated accrual. A second study evaluating the carbonic anhydrase IX (CAIX)-directed antibody girentuximab has recently been reported. CAIX has been related to RCC pathogenesis and may be a biomarker of response to VEGF-directed agents [20,21]. In a phase III trial, 864 patients with pT2NxM0 (Fuhrman grade 3−4), pT3-4NxM0 or PTxN1M0 disease were randomized to receive loading with girentuximab followed by 23 weekly intravenous doses or placebo for the same duration of time [22]. Ultimately, the study failed to achieve its primary endpoint of demonstrating an improvement in DFS. Notably, the study did identify that patients with high levels of CAIX in nephrectomy tissue derived clinical benefit with girentuximab. These findings suggest a potential path for further development of adjuvant girentuximab in a population of patients selected by high CAIX expression.

Finally, a discussion of adjuvant therapy is not complete without noting the highest-risk group of patients — those individuals that have had metastasectomy for limited sites of metastatic disease [23]. Across multiple series, 5-year survival rates in this population vary from 13% to 50% [24]. Although the standard of care following metastasectomy remains vigilant imaging, one study (ECOG 2810) aims to assess the role of targeted therapy in this setting. Specifically, this phase III trial will randomize a total of 180 patients with complete resection of metastatic disease to 1 year of either pazopanib or placebo, with the primary endpoint of DFS.

3.2. Current status of cytoreductive nephrectomy for mRCC

In the era of immunotherapy, the role of cytoreductive was well established. In two identical protocols, 331 patients were randomized to receive IFN-α alone or with cytoreductive nephrectomy [25]. Median OS was 13.6 months in patients receiving cytoreductive nephrectomy, as compared to 7.8 months in the IFN-α alone group ($p = 0.0002$). Correlative studies examining patients who have received cytoreductive nephrectomy show fluxes in certain immune subpopulations following the procedure, such as an increase in natural killer (NK) cells [26]. These changes provide a plausible mechanism for synergy between immunotherapy and surgery.

In the setting of targeted therapies, the role of cytoreductive nephrectomy remains unclear. At present, the practicing urologist must rely largely on retrospective data. An analysis of the Surveillance, Epidemiology and End Results (SEER) database suggested that median OS amongst patients receiving cytoreductive nephrectomy improved from 13 months to 19 months between the time periods of 1993−2004 and 2005−2010, respectively [27]. In patients who did not receive cytoreductive nephrectomy, no significant difference in OS was noted between the two time periods. Notably, the latter period was thought to reflect the targeted therapy era, given that FDA approvals of VEGF- and mTOR-directed agents occurred over this period. A similar interpretation of the SEER data suggesting improved survival with cytoreductive nephrectomy in recent years has been confirmed by other groups [28,29]. Strengths of the SEER database include its size, encompassing nearly 28% of the US population. However, a major limitation is that the database does not provide treatment-related information — thus, the nature of therapy rendered during the two time periods assessed (e.g., targeted therapy *vs.* immunotherapy) is merely an assumption.

A more recent retrospective study reported by the International mRCC Database Consortium provides more granular, patient-level data in a cohort of individuals who had received targeted therapy for mRCC [30]. This database houses records for a total of 1658 patients with synchronous metastatic disease, of whom 982 had cytoreductive nephrectomy. The survival benefit associated with the procedure was profound (20.6 months *vs.* 9.5 months; $p < 0.0001$). A challenge in interpreting this data is an inherent selection bias, as patients may have not received cytoreductive nephrectomy on account of comorbidities or poor performance status. However, even after adjustment for standard prognostic criteria, the hazard ratio for death with cytoreductive nephrectomy was

0.60 (95%CI, 0.52—0.69; $p < 0.0001$). A key finding from the study was that patients with a poor prognosis (specifically, those patients with a projected OS of <12 months) appeared to derive no benefit from the procedure. Although these findings require further validation, they provide perhaps the most robust justification to date for continued use of cytoreductive nephrectomy in patients receiving targeted therapy, perhaps with the exception of patients with poor prognostic criteria.

Two prospective trials are currently underway to assess the utility and timing of cytoreductive nephrectomy, respectively. In the French-led CARMENA trial, a total of 576 patients will be randomized to receive either sunitinib alone or cytoreductive nephrectomy [31]. The primary endpoint of the trial is OS, with secondary endpoints including post-operative morbidity and non-compliance with sunitinib therapy. In EORTC 30073, patients will be randomized to receive either sunitinib followed by cytoreductive nephrectomy, or cytoreductive nephrectomy followed by sunitinib [32]. The study will enroll a total of 458 patients, and will examine the primary endpoint of PFS. Although both CARMENA and EORTC 30073 will provide valuable insights, the studies do suffer from some inherent limitations. Perhaps most importantly, both studies are based on sunitinib. In the current landscape, it is unclear whether the results will be applicable to other potential first-line agents, such as bevacizumab, pazopanib or temsirolimus. Furthermore, with multiple other relevant agents evolving (as discussed in the next section), it is possible that the study results will be antiquated by the time they are available.

3.3. Current status of first-line therapy for mRCC

National Comprehensive Cancer Network (NCCN) guidelines offer several category 1 (i.e., unanimous) recommendations for first-line systemic therapy for mRCC. These include sunitinib, pazopanib and bevacizumab with IFN-α, or temsirolimus in the setting of poor-risk features [33]. Each of these agents is supported by phase III data which has been reviewed extensively in the existing literature. In the clinic, the practicing physician is faced with the

challenge of deciding amongst these agents. Comparative data have emerged in recent years which compare two frequently utilized front-line options, sunitinib and pazopanib. In the COMPARZ trial, 1110 patients with mRCC and no prior treatment were randomized to receive either sunitinib or pazopanib at standard doses [34]. The primary endpoint of the trial was PFS, with secondary endpoints including OS, quality of life (QoL) and safety.

Ultimately, pazopanib was determined to be non-inferior to sunitinib with respect to PFS (HR 1.05, 95%CI 0.90—1.22) [34]. No significant difference in OS was observed across treatment arms. The COMPARZ trial offers a unique opportunity to compare the side effect profile of two distinct VEGF-TKIs. Sunitinib was found to be associated with a greater incidence of fatigue, hand-foot syndrome and thrombocytopenia, while pazopanib was found to have a great incidence of transaminitis. QoL assessments performed during the first 6 months of therapy generally favored pazopanib. Of note, however, these assessments were performed at day 28 of each 42-day cycle. In the context of sunitinib therapy, which is dosed on a 4 week on/ 2 week off schedule, day 28 would presumably be when toxicity peaks. In contrast, treatment with pazopanib remains consistent across the entire 42-day cycle — thus, QoL metric may be somewhat biased in this report.

COMPARZ provides an important benchmark for OS estimates in mRCC. Whereas a median OS of approximately 13 months was quoted in the cytokine era, median OS was 28.3 months and 29.1 months in the pazopanib and sunitinib arms, respectively [35,36]. In the subset of patients with good-risk disease by MSKCC risk criteria, median OS was 42.5 months with pazopanib and 43.6 months with sunitinib. These impressive statistics are critical to factor into forthcoming clinical trials, particularly studies of immunotherapy which hope to demonstrate OS improvement as a primary endpoint.

The practicing urologist should be aware of several studies that may substantially alter the current approach to first-line management (Table 2). Two phase III trials are exploring VEGF-TKI therapy in combination with cancer vaccines. The first explores IMA901, a vaccine comprised of tumor associated peptides (TUMAPs) identified through

Table 2 Planned, ongoing and recently completed trials exploring novel therapies for mRCC in the front-line setting.

Experimental arm	Control arm	n	Primary endpoint	Status
Phase II trials				
Cabozantinib	Sunitinib	150	PFS	Enrollment ongoing (Estimated primary completion: Sep 2017)[b]
MPDL3280A ± Bevacizumab	Sunitinib	150	PFS	Enrollment ongoing (Estimated primary completion: Jan 2016)
Phase III trials				
Sunitinib + IMA901 + cyclophosphamide	Sunitinib	320	OS	Enrollment completed (Estimated primary completion: July 2015)
Sunitinib + AGS-003	Sunitinib	450	OS	Enrollment ongoing (Estimated primary completion: April 2016)
Nivolumab + ipilimumab	[a]	[a]	[a]	Planned

[a] Details not publicly available.
[b] Final data collection date for primary outcome measure.

a screen comparing normal tissue and tumor tissue derived from 32 patients with RCC [37]. In a phase I clinical trial, IMA901 was administered to 15 patients with no prior treatment and 13 patients with multiple prior therapies. At a 3-month benchmark, one partial response (PR) was recorded along with 11 patients with stable disease (SD). Limited toxicities were observed in this initial experience, and correlative studies identified a greater clinical benefit rate amongst patients that elicited a more potent immune response to TUMAPs. A phase II experience of IMA901 was subsequently conducted, exploring IMA901 monotherapy or IMA901 preceded by a single dose of cyclophosphamide. The latter arm explores the hypothesis that "immune priming" with cyclophosphamide may reduce regulatory T-cell (Treg) populations. Ultimately, it was found that cyclophosphamide priming significantly improved survival.

These studies have culminated in a phase III study comparing sunitinib monotherapy to sunitinib with IMA901, the latter arm including a single priming dose of cyclophosphamide [38]. The study enrolled 320 treatment-naïve patients with mRCC who demonstrated favorable- or intermediate-risk disease by Heng criteria. Patients in this experience were randomized to the experimental and control arm in a 3:2 fashion. While the study explored the primary endpoint of OS, several secondary endpoints will focus on correlative aims including characterization of immune response.

A second vaccine therapy currently in late stage development for mRCC is AGS-003, an autologous dendritic cell vaccine. Generation of the vaccine involves harvesting autologous tumor tissue, isolation of RNA and subsequent electroporation of this RNA into dendritic cells [39]. The resulting product is reinfused in the patient at several timepoints. AGS-003 has been explored as both monotherapy and in combination with sunitinib. The latter study included 22 patients with synchronous metastatic disease who had received cytoreductive nephrectomy. All patients in this experience had either intermediate-risk disease (71%) or poor-risk disease (29%) by Memorial Sloan Kettering Cancer Center (MSKCC) criteria. Patients received one cycle of sunitinib followed by 5 doses of AGS-003 every 3 weeks. The observed OS in the overall study population was 30.1 months, well in excess of the projected survival of 15 months estimated by existing nomograms. In particular, those patients with an increase in memory T-cells were noted to have prolonged survival [40].

The phase III ADAPT trial will compare sunitinib monotherapy to sunitinib with AGS-003 in a total of 450 patients with synchronous mRCC [41]. The study aims to achieve a roughly 30% improvement in survival with the addition of AGS-003 as compared to sunitinib monotherapy. Patients will be stratified by the number of adverse risk factors they possess according to the Heng prognostic criteria [42]. It is estimated that the study will complete accrual in 2015.

Outside of vaccines, other immunotherapeutic approaches may potentially alter current first-line treatment algorithms for mRCC. Increasing attention has been focused on the programmed death-1 (PD-1) signaling pathway. PD-1, expressed on the surface of the activated T-cell, may bind to one of two ligands, PD-L1 or PD-L2, on the surface of the antigen presenting cell [43]. Association of these receptors leads to T-cell anergy and diminution of the antitumor immune response — a so-called "immune checkpoint". As monotherapy, the PD-1 inhibitor nivolumab is being explored in a phase III registration trial comparing the agent to everolimus in patients that have received 1—2 prior anti-angiogenic therapies [44]. The study has completed accrual, and results are anticipated in 2015. Although phase II studies of nivolumab suggest modest response rates (roughly 20% across recently reported studies), higher activity has been seen with nivolumab in combination with a distinct checkpoint inhibitor, ipilimumab [45,46]. A phase I study combining two dosing regimens of nivolumab with ipilimumab in 44 patients showed response rates of 29%—39% [47]. Notably, 77% of patients in this experience had received prior treatment. These impressive data prompted announcement of a phase III study exploring the combination of nivolumab with ipilimumab in the front-line setting.

Several other checkpoint inhibitors under development also show promise in mRCC. In a phase I expansion study, MPDL3280A (a PD-L1-directed monoclonal antibody) was administered in 53 patients with mRCC [48]. Of these patients, 83% had received prior therapy. Amongst 47 evaluable patients, a response rate of 13% was observed with a 24-week PFS of 53%. Based on the encouraging efficacy and limited toxicity associated with the agent, a randomized phase II study has emerged including three treatment arms: (1) MPDL3280A monotherapy, (2) sunitinib monotherapy, and (3) MPDL3280A with bevacizumab [49]. The study will include a total of 150 patients with treatment-naïve mRCC, and will explore the primary endpoint of PFS. Crossover onto the combination therapy arm is allowed for patients receiving monotherapy with either MPDL3280A or sunitinib. If data from this study is encouraging, a phase III study exploring this combination is foreseeable.

While there is no doubt that a resurgence of immunotherapy has occurred in recent years, there is still substantial interest in targeted therapies acting upon other axes. The dual VEGFR2/MET inhibitor cabozantinib has shown substantial activity in a phase I trial including heavily pre-treated patients with mRCC [50]. Amongst 25 patients with a median of 2 prior lines of therapy, a median PFS of 12.9 months was observed. A registration trial is currently underway comparing cabozantinib to everolimus in patients with prior VEGF-directed therapy [51]. In the first-line setting, an Alliance-led phase II trial will compare sunitinib and cabozantinib. The study will accrue a total of 150 patients and explore the primary endpoint of PFS [52]. A positive outcome could warrant further exploration of cabozantinib as initial therapy for mRCC.

4. Conclusion

With the rapid evolution of targeted therapies and other novel compounds for RCC, the practicing urologist faces a number of important challenges. In the coming years, it will be critical to follow the adjuvant literature carefully. With multiple trials either recently completed or still underway, there is substantial potential for VEGF-TKIs and mTOR inhibitors to migrate from the setting of metastatic disease to the adjuvant space. Similar attention should be given to the

literature pertaining to cytoreductive nephrectomy. Although the preponderance of studies seem to indicate that the benefit of cytoreductive nephrectomy is maintained in the targeted therapy era, prospective studies such as the CARMENA trial will more firmly establish the role of this modality. Finally, the urologist should be intimately aware of emerging systemic treatments for mRCC, many of which have a foreseeable path into the front-line setting. Some of these therapies (e.g., AGS-003, a vaccine derived from surgically excised tumor tissue) may require a multidisciplinary approach for administration.

Conflicts of interest

The authors declare no conflict of interest.

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