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Therapeutic challenges in advanced renal cell carcinoma

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SUMMARY

The therapeutic landscape of advanced renal cell carcinoma has grown increasingly more complex with the recent approval of several molecularly targeted agents. While researchers focus on developing predictive algorithms and identifying novel therapeutic targets and agents, clinical practitioners continue to face many practical challenges when determining therapeutic strategies for individual patients. This review will discuss several of these challenges including patient selection strategies, sequential therapy, optimal dose and schedule of various drugs, and therapeutic options for patients with nonclear-cell renal cell carcinoma.

With several new agents receiving approval by the US FDA over the past few years, there have been many new additions to the therapeutic landscape of advanced renal cell carcinoma (RCC). It appears clear that in this era of targeted therapies, the numerous therapeutic options in RCC have translated into improved outcomes and survival for patients [1]. Despite these recent advancements, many therapeutic challenges persist for oncologists treating patients with advanced RCC. These include patient selection strategies, predictive algorithms, optimal dose and schedule of agents, determining the most appropriate sequence of agents and therapeutic options for patients with nonclear-cell RCC. This review will be focus on these practical challenges facing practitioners.

Patient selection strategies

Although randomized Phase III trials have provided guidance for the average patient in specific clinical situations, individual patients and tumors have distinct characteristics that may greatly influence their response to specific therapies. Unfortunately, although there has been promising progress, no predictive biomarkers have yet been prospectively validated in RCC therapeutics. Nonetheless, with so many different therapeutic options available, identification of predictive biomarkers and development of patient selection models remains one of the highest research priorities of the field. In the future, efforts in this regard will face the challenge of combining clinical features of the patient with pathologic, molecular and genetic information from tumor specimens (both from primary and metastatic lesions) and incorporating ever-emerging technology platforms. In the meantime, however, clinical practitioners treating patients with advanced RCC face the challenge of selecting the most appropriate treatment for their individual patients in the absence of validated predictive models.

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First-line therapy

With five molecularly targeted agents (sorafenib, sunitinib, temsirolimus, pazopanib and evacizumab plus IFN-α) approved for advanced RCC regardless of treatment setting, the selection of the most appropriate agent for patients with advanced clear-cell RCC can be a perplexing challenge for practitioners (Table 1). This is made more complicated by the persistence of high-dose (HD) IL-2 as a viable therapeutic option for appropriately selected patients. Some guidance is made available through recommendations provided by the National Comprehensive Cancer Network (NCCN) [2]. Based on the results of large Phase III trials, the NCCN currently gives a category 1 recommendation to sunitinib, pazopanib and bevacizumab/IFN-α, along with a category 2A recommendation to sorafenib in patients with predominantly clear-cell, advanced RCC [3–6]. The NCCN also gives a category 1 recommendation to temsirolimus for the treatment of poor prognosis patients (≥three out of six well-described poor prognostic features including: Karnofsky performance status <80, time from diagnosis to randomization <12 months, serum lactate dehydrogenase >1.5 upper limit of normal, hemoglobin < lower limit of normal, corrected serum calcium >10 mg/dl and >one metastatic site) with predominantly clear-cell RCC [7]. Finally, the NCCN gives HD IL-2 a category 2A recommendation for appropriately selected patients with predominantly clear-cell RCC.

With these guidelines in mind, when determining the most appropriate first-line treatment for patients requiring therapy for advanced clear-cell RCC, the practitioner should first determine if the patient might be eligible for immunotherapy. Although recent Phase III trials have effectively removed single-agent interferon molecules from the RCC treatment algorithm, there remains a subset of patients who derive significant and clinical benefits from immunotherapy and for whom omitting this therapy might greatly compromise their long-term treatment outcome. Recent studies suggest that in the current era, response to HD IL-2 exceeds 25%, with at least 10% of patients exhibiting complete responses that last in excess of 2 years [8]. Studies also suggest that molecularly targeted therapies have substantial activity in cytokine-refractory patients, while the converse (activity of IL-2 following molecularly targeted agents) may not be true [9–13]. The decision to refer a patient for HD IL-2 is typically based on many factors ranging from clinical (e.g., younger patients, clear-cell histology, good prognosis, good performance status, disease that is not rapidly growing or few medical comorbidities), practical (availability and proximity to IL-2 specialty centers) and patient motivation. Therefore, it remains practice to first consider appropriate patients for either HD IL-2 or another novel immunotherapy prior to considering therapy with molecularly targeted agents.

Once a decision has been made with respect to immunotherapy, the choice of molecularly targeted agents remains challenging. The collective experience and ability to tailor specific therapies to individual patients has been historically limited by the lack of comparative trials among FDA-approved agents. For example, although temsirolimus is approved and recommended for patients with poor prognosis, it is not clear if an agent such as sunitinib may not have similar, or even superior, activity in this setting. Thankfully, some guidance is now available from the recently reported COMPARZ trial; a Phase III trial in which 1110 previously untreated patients with advanced RCC were randomized in a 1:1 fashion to receive either sunitinib or pazopanib with a primary end point of progression-free survival (PFS) [14]. In terms of efficacy, pazopanib was found to be noninferior to sunitinib, with a median PFS of 8.4 versus 9.5 months (hazard ratio: 1.05; 95% CI: 0.90–1.22). Treatment with pazopanib was associated with lower reported rates of fatigue (55 vs 63%, any grade); hand–foot syndrome (29 vs 50%), taste alteration (26 vs 36%), dyspepsia (14 vs 24%), hypothyroidism (12 vs 24%), mucositis (11 vs 26%), neutropenia (11 vs 27%), thrombocytopenia (10 vs 34%) and anemia (7 vs 19%) compared with treatment with sunitinib. Pazopanib did have higher reported rates of alanine aminotransferase elevation (31

vs 18%) and aspartate aminotransferase elevation (27 vs 18%) compared with sunitinib. Overall, pazopanib was felt to have shown a significant difference regarding safety and quality of life. Indeed, in a recent patient preference study performed as an adjunct to the COMPARZ trial, in which patients were randomized to receive pazopanib or sunitinib, Escudier and colleagues reported a significant preference in favor of pazopanib with the most commonly cited reasons of superior quality of life and less fatigue [15]. Therefore, based on these recent data, practitioners might favor sunitinib for patients with underlying liver dysfunction and good baseline performance status and favor pazopanib for patients with baseline fatigue, cytopenias and minimal tolerance for toxicities. The first-line therapeutic setting will likely become even more complicated by the possible approval of tivozanib, which recently demonstrated superior PFS and objective response rate compared with sorafenib in a randomized Phase III trial in patients with advanced RCC who had not had prior molecularly targeted therapy [16] (although a recent press release suggests that overall survival is not superior [101]). Ultimately, however, in the absence of data from comparative Phase III trials among all of the available agents, the decision for first-line molecularly targeted agents will likely be based as much on individual practitioner preference (e.g., comfort and familiarity with drug dosing and side effect management, mode of administration among others) as on any treatment algorithms.

Second-line therapy

Much like first-line therapy, the choice of a second-line therapy can be similarly confusing. For the small subset of patients treated initially with HD IL-2, given the aforementioned efficacy of molecularly targeted therapies in the cytokine-refractory population, the choice for second-line therapy may be very similar to the choice of a first-line molecularly targeted agent. In addition to the molecularly targeted therapies approved in the first-line setting, another agent that has demonstrated particular efficacy in the cytokine-refractory setting is axitinib. In the recently reported AXIS trial, in which 723 patients with advanced RCC who had failed one prior systemic therapy were randomized to receive either sorafenib or axitinib; the PFS in patients who had failed prior cytokine therapy and were randomized to receive axitinib was 12.1 months (compared with 6.5 months for sorafenib) [17]. Therefore, axitinib must be considered as a primary therapeutic option for those patients immediately following cytokine failure.

For the more common clinical scenario of a patient who has failed a first-line VEGF-targeted agent, practitioners are again faced with a plethora of therapeutic options. Based on large Phase III trials, the NCCN currently provides both axitinib and everolimus category 1 recommendations in the second-line setting (axitinib for patients who have failed any prior therapy and everolimus specifically for those who have a failed a VEGF–tyrosine kinase inhibitor [TKI]) (Table 1) [17,18]. Furthermore, retrospective analysis has made it clear that there is no definitive cross-resistance between agents such as sunitnib, sorafenib and bevacizumab/IFN-α, and these agents remain therapeutic options following initial TKI failure [19]. In essence, the primary decision a practitioner must make in this scenario is whether to continue VEGF-targeted therapy with another TKI or change to a different class of agents (i.e., an mTOR inhibitor). While both strategies are supported by Phase III data, there is little guidance in deciding between the two. The only large comparative study in this scenario is the INTORSECT trial, a Phase III study in which 480 RCC patients failing sunitinib are randomized to receive either sorafenib or temsirolimus. The results from this trial have yet to be reported and will be limited by the fact that temsirolimus is not approved in the second-line setting.

Therefore, the practitioner once again must integrate available clinical data with patient-specific factors. It is possible that some guidance might be derived from how the patient tolerated their prior therapy. For example, patients who may have suffered from VEGF

receptor (VEGFR)–TKI specific toxicities, such as refractory hypertension, proteinuria, cardiac complications or diarrhea, might benefit from changing to mTOR inhibitors. Patients who have tolerated VEGFR–TKI well or with nonspecific symptoms, such as fatigue, should perhaps consider alternate or more potent VEGFR–TKI therapy (e.g., axitinib). It is also possible that some guidance might be gleaned from how patients responded to their prior therapy. Results in this regard have been conflicting to date. One large retrospective analysis of patients treated with first-line VEGF-targeted therapy found no clear correlation between PFS on first-line therapy and PFS on second-line therapy [20]. However, in the recently reported secondary end point analysis of the Phase III AXIS trial, Rini *et al.* reported that the median PFS for patients whose duration of prior sunitinib therapy was ≥9 months was significantly longer than those whose prior sunitinib duration was <9 months for both sorafenib (4.6 vs 2.9 months) and axitinib (6.3 vs 4.5 months) arms [21]. While this finding must be validated prospectively and independently, in the absence of other predictive models, it is not unreasonable to consider continuing VEGFR–TKI therapy in patients who appear to have had either substantial or prolonged responses to their prior VEGFR–TKI therapy and consider changing those patients who were either primarily refractory or had very brief or minor responses to their prior VEGFR–TKI therapy to mTOR inhibitors.

Sequential therapy

Thus far, no combination of molecularly targeted agents have proven clearly superior to single-agent therapy. While it remains hopeful that rationale combinational therapy will ultimately lead to improved clinical outcomes, until that time, many investigators have focused on determining the optimal sequence of agents to maximize the duration of disease control. This premise is based on several clinical observations. First, as discussed earlier, it is clear that both VEGF-targeted agents and mTOR inhibitors are active following failure of cytokine-based therapy [9–12]. Second, also mentioned previously, a small retrospective analysis has suggested that HD IL-2 therapy should be considered as the initial treatment rather than following TKI [13]. Furthermore, both retrospective analyses and prospective clinical trials have suggested that VEGF pathway inhibitors may have activity following disease progression on other VEGF (or even the same) pathway inhibitors [19,22–25]. Finally, analysis of the RECORD-1 study suggests that everolimus may have similar activity after the failure of two VEGF–TKI therapies as after one VEGF–TKI therapy [26].

Hence, despite our efforts, there is not a clearly defined optimal sequence of agents and the most current clinical data support both sequences of TKI–TKI–mTOR inhibitor and TKI–mTOR inhibitor–TKI. In the absence of prospective data, the practitioner must individualize each decision regarding sequence. For example, an intervening mTOR inhibitor between VEGFR–TKI may provide a valuable break for patients suffering from TKI-specific toxicities. Conversely, as clinical data suggests that the efficacy of mTOR inhibitors is similar following failure of one or two TKIs, a second-line VEGFR–TKI might be indicated in patients who are tolerating their first-line VEGFR–TKI well. Several clinical trials are currently underway to address the value of specific therapeutic sequences in RCC and this remains an active area of clinical research. Hopefully, over the coming years, these efforts will provide some broader guidance regarding the possibility of optimal therapeutic sequences in patients with advanced RCC.

Optimal dose & schedule of agents

The determination of the standard dose and schedule for molecularly targeted agents is largely determined empirically in Phase I and II trials. However, the optimal dose derived from dose-limiting toxicities observed in a handful of patients may not be the optimal dose

for each individual patient. Many lines of investigation have suggested that not all patients are receiving their individual optimal dose with various agents. Houk *et al.* determined that higher steady-state area under curve of total drug (sunitinib and its active metabolite, SU12662) was significantly associated with longer time to tumor progression, higher response rate, improved overall survival and higher diastolic blood pressure [27]. Similarly, in a retrospective analysis Rini *et al.* also showed that both higher area under curve of drug and incidence of diastolic hypertension were associated with a longer PFS in patients treated with axitinib [28]. These results support the hypothesis that adequate drug levels are necessary to experience the maximal therapeutic benefit with VEGFR–TKI and also suggest that hypertension might represent a surrogate marker for VEGFR–TKI blood levels. The clinical utility of escalation of drug dose until hypertension is being investigated in a trial in which patients without hypertension after an initial 4 weeks of axitinib therapy are randomly assigned to receive either additional axitinib or placebo (NCT00835978 [102]). In the meantime, practitioners should be aware of the possibility that patients who experience disease progression on VEGF targeted agents without experiencing hypertension (or other significant toxicities) may not be achieving adequate drug levels.

In addition to dose escalation, it is possible that intermittent dosing schedules might allow for higher peak drug concentrations, while possibly minimizing toxicity. One example of this is the modulation of sunitinib treatment schedule, which was recently assessed prospectively in a Phase II trial in which 292 patients with advanced RCC were randomized to receive sunitinib at the standard treatment schedule (50 mg/day for 4 weeks followed by 2 weeks off treatment) versus continuously at a dose of 37.5 mg/day [29]. Patients treated with the continuous treatment regimen experienced a trend towards inferior time to tumor progression (median: 7.1 vs 9.9 months; hazard ratio: 0.77; 95% CI: 0.57–1.04; $p = 0.09$) with similar overall survival and adverse event profiles observed for both regimens. While the final conclusion of this study was that the intermittent dosing regimen should remain the standard dosing regimen, the results illustrate that the dosing schedule may play as important a role as drug dose with some agents. How these results might influence treatment schedule considerations for other VEGFR inhibitors in patients with RCC is an area of potential future investigation. In the meantime, however, practitioners should continue to favor the standard dosing schedules of available agents and adjust schedules and doses primarily to alleviate toxicity rather than to gain additional efficacy.

Therapy for nonclear-cell RCC

While treatment for patients with RCC of clear-cell histology is made more complicated by a surfeit of therapeutic options, there remains no clear standard therapies for patients with nonclear-cell RCC. Of the molecularly targeted agents, only temsirolimus has been studied in a randomized Phase III trial allowing patients with nonclear-cell histology [7]. Upon subanalysis of this Phase III trial, among the 73 patients with nonclear-cell histology (75% of which had the papillary subtype) randomized to receive either temsirolimus ($n = 36$) or interferon ($n = 37$), the median overall survival of patients was 11.6 months in the temsirolimus group versus 4.3 months in the interferon group [30]. For this reason, temsirolimus was given a category 1 recommendation by the NCCN for the treatment of patients with metastatic nonclear-cell RCC. Data for the efficacy of other agents in nonclear-cell RCC is less complete. Sorafenib and sunitinib have both demonstrated efficacy and safety in patients with nonclear-cell histology in their respective expanded access programs and, based on these data, are given category 2A recommendations by the NCCN [31,32]. Several clinical trials are ongoing in patients with nonclear-cell RCC. Potentially, the most informative may be several randomized Phase II trials noted in Table 2 comparing mTOR inhibitors with VEGF antagonists.

It is possible that the lack of clarity regarding treatments for nonclear-cell RCC may at least be in part due to the tendency to investigate all nonclear-cell histologies as a single group. It is clear that the various histologic subtypes (papillary type I and II, chromophobe and collecting duct) are characterized by distinct molecular biologies. For example, sporadic papillary type I RCC are sometimes characterized by activating mutations in *c-Met*, whereas loss of fumarate hydratase is characteristic of at least the hereditary form of papillary type II RCC. These molecular distinctions may be clinically relevant as illustrated by a recent Phase II trial of sunitinib in patients with nonclear-cell RCC, which suggests a differential response rate among the histologies, with two out of five patients with chromophobe subtype (median PFS: 12.7 months) versus zero out of 27 patients with papillary subtype (median PFS: 1.7 months) experiencing a partial response by Response Evaluation Criteria in Solid Tumors [33]. It is likely that it would be ideal, if somewhat infeasible given the paucity of certain histologic subtypes, if the various RCC histologic groups could be investigated separately. In the meantime, practitioners should at least consider the histologic subtype in their decision-making. For example, clinical data supports the use of temsirolimus as a first-line agent for nonclear-cell RCC, particularly the papillary subtype, while there is some suggestion that VEGFR–TKI may have a unique efficacy in the chromophobe subtype. Looking forward, given the unique molecular biology of each histologic subtypes, more effective therapies will likely require the identification of novel therapeutic targets followed by the development of appropriately targeted therapies.

Conclusion & future perspective

Individualized therapy for patients with advanced RCC has become nuanced by the broad availability of many molecularly targeted agents and increasing awareness of interpatient heterogeneity, with respect to response and tolerance to these therapies. This complexity will almost assuredly increase in the upcoming years with the possible approval of yet another VEGFR-targeted TKI (tivozanib) in the first-line setting and the likelihood of many novel therapeutic agents, such as the PD-1 antibody MDX-1106, entering Phase III trials. Within this environment, RCC researchers will continue to be focused on the identification of patient selection models incorporating traditional clinical, pathologic and histologic factors along with data made available through emerging technology platforms (e.g., whole-genome sequencing). Practitioners treating patients with RCC face the challenge of staying abreast of these scientific and therapeutic developments while providing individualized therapy for their patients. As prospective data are emerging with respect to critical therapeutic issues, such as predictive biomarkers of response and optimal dose, schedule and sequence of various therapies, practitioners should be prepared to rapidly incorporate these developments into clinical practice and hopefully witness improved clinical outcomes.

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Practice Points

- Although several agents are recommended by the National Comprehensive Cancer Network for first-line therapy of patients with advanced renal cell carcinoma (RCC), the choice of specific therapy should be individualized to specific clinical and pathologic factors.
- The choice of a second-line agent for patients with advanced RCC can partly be based on how the patient responds to first-line therapy with respect to toxicity and efficacy.
- There are currently no validated predictive biomarkers of response for any therapy in advanced RCC.
- Practitioners should be aware of the existence of significant interpatient heterogeneity with respect to the concentration of drug achieved in the blood with various therapies at standard doses, suggesting that in certain cases both dose and schedule might be individualized.
- Practitioners should take into account specific histology when choosing a therapy for patients with nonclear-cell RCC.

Table 1

Currently approved molecularly targeted agents in renal cell carcinoma.

Drug	Molecular target	National Comprehensive Cancer Network recommendation
Sorafenib (Nexavar®)	TKI against VEGF receptor 2, PDGF receptor, c-Kit, BRAF, c-Raf	Category 2A for first-line therapy of selected patients; category 1 following cytokines, and category 2A following other TKIs for predominantly clear-cell RCC
Sunitinib (Sutent®)	TKI against VEGF receptor 2, PDGF receptor, c-Kit,	Category 1 for first-line therapy and following cytokines, and category 2A following other TKIs for predominantly clear-cell RCC
Bevacizumab (plus IFN-α; Avastin®)	Monoclonal antibody against VEGF	Category 1 for first-line therapy for predominantly clear-cell RCC; single-agent bevacizumab category 2A following cytokines
Pazopanib (Votrient®)	TKI against VEGF receptor 2, PDGF receptor and c-KIT	Category 1 for first-line therapy; category 1 following cytokines, and category 3 following other TKIs for predominantly clear-cell RCC
Axitinib (Inlyta®)	TKI against VEGF receptor 2, PDGF receptor and c-KIT	Category 1 following any other approved therapy for predominantly clear-cell RCC
Temsirolimus (Torisel®)	Allosteric inhibitor of mTOR (intravenous)	Category 1 for first-line therapy of poor prognosis patients; category 2A following cytokines and category 2B following TKIs for predominantly clear-cell RCC; category 1 for poor prognosis and category 2A for others with nonclear-cell histology
Everolimus (Affinitor®)	Allosteric inhibitor of mTOR (oral)	Category 1 following TKI for predominantly clear-cell RCC

RCC: Renal cell carcinoma; TKI: Tyrosine kinase inhibitor.

Table 2

Important clinical trials in nonclear-cell renal cell carcinoma.

Trial title	Phase	ClinicalTrials.gov identifier	Sponsor	Ref.
Everolimus vs sunitinib in Ncc-RCC	II	NCT01185366	MD Anderson	[103]
Study in Ncc-RCC temsirolimus vs sunitinib	II	NCT00979966	Central European Society for Advanced Cancer Research	[104]
Phase II study of afinitor vs sutent in patients with metastatic Ncc-RCC	II	NCT01108445	Duke University	[105]
Everolimus and bevacizumab in advanced Ncc-RCC	II	NCT01399918	Memorial Sloan Kettering	[106]

Ncc-RCC: Nonclear-cell renal cell carcinoma.