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The Future of Kidney Cancer Treatment

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Introduction

Despite the progress that has been made in renal cell carcinoma (RCC), there are still many unmet needs to be addressed. This article will focus on the opportunities and challenges in emerging clinical trials of adjuvant therapy and predictive biomarkers, and in first-line and previously treated metastatic RCC. In addition, we will discuss what clinical outcomes we are not measuring in patients, and how to improve patient care in the future. Finally, this article will discuss unmet needs in RCC that are imminently attainable.

Emerging Clinical Trials

Adjuvant Treatment

For RCC, the current standard of care for adjuvant treatment is limited to observation or a clinical trial. In the past few years, there have been many randomized phase 3 trials either completed, near completion, or in progress, and this creates a tremendous resource for patients. Unfortunately, the ASSURE study—comparing 1 year of adjuvant sunitinib (Sutent, Pfizer) vs sorafenib (Nexavar, Bayer/Onyx) vs placebo—was not positive.[1] However, there are 5 more ongoing studies whose results are still pending (see the table).

One potential problem with these studies is that they all use similar strategies, including a relatively limited duration and dosage of therapy. Furthermore, all of the treatments (except everolimus in the EVEREST study) are monotherapies of vascular endothelial growth factor receptor (VEGFR)–targeted tyrosine kinase inhibitors (TKIs), which is not the traditional cytotoxic approach that has been established in the adjuvant setting of many other solid tumors.

One of the biggest concerns in the adjuvant setting is that most studies select patients using grade and stage, which do not always correlate with biology. The biology likely becomes more heterogeneous as these patients advance in grade and stage. Because the current studies are examining a diffuse population of tumors, showing a significant benefit may be difficult even if a subset of patients are exquisitely sensitive to inhibition of this VEGF pathway.

Despite these concerns, there is still a tremendous opportunity to learn from these studies, even if the results

Table. Ongoing Clinical Trials for the Treatment of RCC

Trial Name	Treatment	Trial Number
Adjuvant treatment		
S-TRAC	Sunitinib vs placebo	NCT00375674
SORCE	Sorafenib vs placebo	NCT00492258
PROTECT	Pazopanib vs placebo	NCT01235962
EVEREST	Everolimus vs placebo	NCT01120249
ATLAS	Axitinib vs placebo	NCT01599754
Untreated metastatic RCC		
CheckMate 214	Nivolumab + ipilimumab vs sunitinib	NCT02231749
CaboSun	Cabozantinib vs sunitinib	NCT01835158
WO29074	MPDL3280A ± bevacizumab vs sunitinib	NCT01984242
ADAPT	AGS003 + SOC vs SOC	NCT01582672
Previously treated metastatic RCC		
METEOR	Cabozantinib vs everolimus	NCT01865747
CheckMate 025	Nivolumab vs everolimus	NCT01668784

RCC, renal call carcinoma; SOC, standard of care.

are negative. The fact that several studies are being conducted will give us an opportunity to explore and validate potential predictors to determine which patients will benefit from these strategies.

Treatment for Metastatic RCC

The National Comprehensive Cancer Network (NCCN) guidelines for treating patients with untreated metastatic RCC have not changed in 6 years. This suggests that, despite the progress made in drug approvals, new study results are not changing the standard of care. However, the current landscape of randomized trials may change that.

There are currently a number of ongoing phase 3 and randomized phase 2 studies that involve novel agents and combinations (see the table). CheckMate 214 (NCT02231749) is examining a combination of checkpoint inhibitors, including the programmed cell death 1 (PD-1) inhibitor nivolumab (Opdivo, Bristol-Myers Squibb) and the cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) inhibitor ipilimumab (Yervoy, Bristol-Myers Squibb). The CaboSun trial (NCT01835158) is treating a higher-risk population of patients with cabozantinib (Cometriq, Exelixis), a multitargeted VEGFR TKI that also inhibits MET. The WO29074 study (NCT01984242) is examining the combination of bevacizumab (Avastin, Genentech) and the programmed death ligand 1 (PD-L1) antibody MPDL3280A vs PD-L1 inhibition alone. Finally, in the ADAPT study (NCT01582672), tumors resected from patients in a debulking nephrectomy are being used to create an autologous vaccine for patients.

The key outcome of these studies is whether immunotherapy represents a paradigm shift in the way we treat RCC. These clinical trials ask 2 questions: (1) Is there a group of patients who would benefit more from upfront immunotherapy than from VEGF-targeted therapy? (2) Is there a group of patients in whom the combination of immunotherapy and VEGF-targeted therapy would be beneficial?

One problem with the trials is that many are not selecting patients based on biology; it is difficult to observe significance if only a subset of patients is responsive to therapy. Another concern is whether improvements in progression-free survival justify any additional toxicity. Hopefully, these studies will find a patient population that benefits from these treatments, along with a strategy to enrich for those patients.

Previously Treated Metastatic RCC

For previously treated metastatic RCC, there have not been any changes in the NCCN guidelines for 4 years, so clearly it is time for progress. Two studies are particularly exciting, the METEOR study (NCT01865747) comparing cabozantinib vs everolimus (Afinitor, Novartis), and the CheckMate 025 study (NCT01668784) comparing nivolumab vs everolimus (see the table). Both studies should provide results over the next year.

The challenges of these studies are similar to those mentioned previously. The benefits of progression-free survival vs toxicity must be assessed, and it may be necessary to focus on a subset of patients who respond well to these drugs. To address this, the CheckMate 025 study is examining whether the checkpoint inhibitor nivolumab is more beneficial in a subset of patients.

Sequential and Combination Strategies

The real challenge going forward is not how to develop the next therapeutic cocktail; it is how to incorporate new therapies in a patient population that is struggling with the current standard of care. Many patients are not able to tolerate the current therapies, including the VEGFR-targeted TKIs, and more research is needed to understand which patients are benefiting, which are struggling, and which may be able to benefit from combination therapy.

One possible strategy to solve this problem is to apply the emerging RCC biology in the clinic today. Biomarkers may not be ready for standard use, but it is necessary to explore them in the context of emerging phase 3 studies. This will improve our understanding of tumor and patient heterogeneity, and allow us to proactively mitigate toxicity by understanding which patients are at risk and what factors influence that risk.

Predictive Biomarkers

A number of prognostic models exist for RCC; however, predictive factors—characteristics that estimate the chance of improvement with a particular therapy—are still desperately needed. Currently, there are several potential candidates, but I will focus on 3 examples: treatment-induced hypertension for VEGF pathway inhibition, the plasma biomarkers interleukin 6 (IL-6) and hepatocyte growth factor (HGF) for VEGF pathway inhibition, and the plasma biomarker lactate dehydrogenase (LDH) for mammalian target of rapamycin (mTOR) inhibition.

Hypertension and VEGF Pathway Inhibition

Many studies have confirmed an association between hypertension induced by VEGFR inhibition and clinical benefit, particularly a benefit in overall survival. One study pooled analyses on axitinib (Inlyta, Pfizer) in multiple types of solid tumors, including RCC.[2] This study found a dramatic improvement in overall survival for the patients who had an elevation in diastolic blood pressure. There were also improvements in progression-free survival and in the overall response rate.

This response was also seen in RCC with sunitinib, another VEGFR-targeted TKI.[3] One study that pooled

phase 3 trials showed that approximately 25% of patients did not develop hypertension. More studies have examined other VEGF pathway inhibitors, including bevacizumab, in multiple tumor types and have found significant improvements in overall survival and progression-free survival in patients who developed hypertension.[4-6]

Despite these data, there are still several obstacles to using hypertension as a predictive factor in a real-world setting. First, we cannot predict up front who will not have an elevation in blood pressure. Second, we do not know how long physicians should wait before deciding that a patient's blood pressure is not increasing. Furthermore, it is possible that a patient's blood pressure is too well controlled to begin with, or that other factors are mitigating blood pressure increases. However, these data are highly reproducible and the overall survival difference is dramatic. In the future, prospective trials should test whether patients who do not experience elevated blood pressure can benefit from VEGF-targeted therapies.

One solution may lie in the use of emerging technology to track blood pressure for studies such as this. An ongoing pilot study at Duke is investigating patients with RCC initiating VEGF-targeted therapy and studying blood pressure using a mobile app on patients' phones. Patients can measure a variety of health-related characteristics on a daily basis, including the number of steps taken, blood pressure, exercise, weight, etc. This is done at home, and the data are automatically downloaded onto their app, which puts the information into an electronic medical record that physicians can see wherever they are. This way, physicians can quickly assess adherence and blood pressure trends in real time. This technology is not expensive and is widely available, so there is no reason this could not be incorporated into multiple prospective studies.

IL-6 and HGF for VEGF Pathway Inhibition

Several plasma biomarkers have also been shown to predict for VEGF treatment efficacy. One study examined multiple plasma biomarkers for their predictive and prognostic value with pazopanib (Votrient, GlaxoSmithKline) treatment, and found that IL-6 levels were both prognostic and predictive for overall survival.[7] Patients with low IL-6 levels had a better prognosis than patients with high IL-6 levels. However, patients with high IL-6 levels had the greatest overall survival benefit from pazopanib treatment. The patients with low IL-6 levels had an improvement in progression-free survival with pazopanib vs placebo, but no difference in overall survival. This suggests that perhaps those patients receiving placebo were able to cross over to VEGF-targeted therapy and gain an improvement in survival equivalent to those treated initially with pazopanib. By contrast, the patients with high IL-6 levels benefited from the immediate use of the VEGF-targeted therapy over placebo, suggesting that this poor-risk population did not have time to progress and then switch over to active therapy. This study also found other factors that clustered together with IL-6 expression; for example, HGF expression. When all 6 of these clustered factors were combined, they formed a more powerful predictor.

Our Alliance cooperative group performed a similar analysis using interferon treatment with or without bevacizumab.[8] The study as a whole did not show a difference in overall survival. However, after using a proportional hazards model to examine whether a distinct population of patients had an overall survival benefit, we found 2 factors to be prognostic, IL-6 and HGF. Our findings recapitulated those of the previous study and further demonstrated that patients with high HGF levels had no benefit from VEGF inhibition. More prospective studies should be done to elucidate the role of HGF as a predictive factor.

Though both were retrospective studies, 2 large, independent, phase 3 studies from different groups have identified the same markers with similar biologic effects. This is very compelling evidence that these 2 factors are predictors of which patients might benefit from VEGF-targeted therapy.

LDH and mTOR Treatment

A study comparing temsirolimus (Torisel, Wyeth) alone, interferon alone, and both in combination found that patients with high LDH levels had a significant improvement in overall survival when treated with temsirolimus.[9] Patients with normal LDH levels had no difference in overall survival. Although patients with high LDH had worse survival overall, it still appears that LDH is predictive. Using a multivariate model, the interaction between high LDH and treatment had a hazard ratio of 0.55 and a doubling of the overall survival, indicating a significant treatment effect.

In the future, we must confirm that these factors are predictive and determine whether they will allow us to better select patients for treatment. We need more studies to validate this, especially prospective phase 3 studies with these factors embedded.

Clinical Outcomes

Multiple clinical outcomes are not currently being measured, but are clearly affecting patient's quality of life. One example is fatigue. Although fatigue is covered in patient-reported outcomes, the measures are qualitative and self-reported. There are better ways to quantify fatigue that should be considered in the future, because approximately half of the patients do not continue to second-line therapy, and half of those do not continue to third-line therapy; this may be due to toxicities that we are not measuring.

Another example is cardiovascular toxicity, which likely is underestimated by our current measures and limits the patient's ability to tolerate drug combinations.

The COMPARZ study (NCT00720941),[10] which examined pazopanib and sunitinib for RCC, found that 13% and 11% of patients, respectively, met the criteria for symptomatic or clinically significant cardiac dysfunction. Although the numbers are still relatively low, they are clinically relevant. This study examined cardiac dysfunction at rest, and therefore these estimates are likely gross underestimates of the dysfunction present with activity. Decompensation at rest occurs only when all other compensatory mechanisms have been exhausted and there is absolutely no capacity to tolerate any kind of exertion.

Fortunately, there are ways to objectively quantify cardiovascular toxicities with activity. For example, a study[11] in breast cancer patients after surgery evaluated the effects of adjuvant doxorubicin chemotherapy on cardiovascular function at rest with 2D echocardiography and found no difference between the treatment and control groups. However, with 3D echocardiography, the researchers found a significant decrease in cardiac function after treatment with chemotherapy. This result is even more profound when patients were evaluated following maximum exercise tolerance, measured by the VO_2 peak. These results tell a completely different story compared with the resting 2D echocardiography data and suggest there is more cardiac dysfunction present than previously recognized.

Checking a resting echocardiogram only underestimates cardiovascular concerns. This toxicity will also limit the ability to add other agents, even relatively nontoxic agents, to this population. Furthermore, these results are for short periods, and some patients are on therapy for years. Novel assessments of patient toxicity are needed to determine who can tolerate long-term VEGFR TKIs, to mitigate decline with exercise or new agents, to develop predictors of toxicity, and to better select patients for combination therapies.

Unmet Needs

Moving forward, there are 6 very important unmet needs in RCC that are imminently attainable: (1) determining the mechanisms of immune escape specific to RCC in order to find targets for immunotherapy, (2) developing and validating tumor-based predictive markers, (3) creating an international registry that includes tissue and imaging outcomes, (4) developing genetically engineered mouse models that recapitulate biology, (5) developing molecular and genetic characterization of non–clear cell RCC, including targeted therapies, and (6) identifying the therapeutic downstream targets of known tumor suppressor genes. Addressing these ares are beyond the scope of this manuscript, but ongoing and emerging data support that each of these areas are attainable in the near future.

Conclusion

The ongoing pivotal trials will be critical resources in the future. However, progress is at risk if we do not understand how to select patients for VEGF-targeted therapies, use more sophisticated tools, and mitigate toxicity. Emerging predictive markers must be embedded in clinical research, even if they are not fully validated. Finally, we must be able to address some of these unmet needs that are immediately attainable.

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