The Right Drug for the Right Patient: Navigating Systemic Therapy Options in Metastatic Renal Cell Carcinoma and Future Directions

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Targeted therapies have changed the landscape of metastatic renal cell carcinoma (mRCC), with a current median survival of approximately 30 months reported in contemporary trials, representing a drastic improvement over the 12- to 13-month overall survival (OS) in the cytokines era. Drugs that target vascular endothelial growth factor (VEGF), VEGF receptor (VEGFR), and mTOR inhibitors have shown success in the clinic. In the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Kidney Cancer, the choice for “best option” is based on the published level of evidence and NCCN panel member consensus. Nevertheless, pointing toward one ideal therapy remains challenging in many cases. New directions in targets and trials are focusing on agents that target mechanisms of resistance to targeted therapy and immune checkpoint blockers with the hope that the next few years will bring more drugs with high levels of evidence and value in the care of patients with mRCC.

How to Choose First-Line and Subsequent Therapies

Currently, the choice of therapy is first and foremost based on the strength of the clinical data in terms of efficacy, often using progression-free survival (PFS) as the clinical end point. Randomized phase III clinical trials represent the backbone for category 1 recommendations in the NCCN Guidelines. These appropriately powered studies compare an experimental single agent or combination therapy with the existing or acceptable standard. For systemic therapy–naïve patients with mRCC, “optimal” first-line options include sunitinib, pazopanib, the combination of bevacizumab and interferon-alpha, and temsirolimus (in poor-risk RCC only). These recommendations are all based on significantly improving efficacy over the control arm, interferon-alpha, or placebo. However, this “embarrassment of riches” regarding recommendations may leave the practicing physician puzzled, mainly because most of these options have not been compared head-to-head, and even when compared, some were proved noninferior in terms of efficacy.

Despite that, the 2 phase II trials share in common that both were conducted in the salvage setting, and the timing they were conducted in, the control groups, and the lines of therapy allowed were quite dissimilar between the new trial and the previous pivotal trials. Both studies included extensive quality of life (QoL) data, but the absence of head-to-head comparisons between both agents limit QoL data interpretation.
Alternative schedules of certain drugs, such as sunitinib, are emerging as a way to provide maximal time on therapy to limit the high rate of treatment discontinuation due to adverse events (especially outside clinical trials). However, the data remain of lower quality, and the comparison cannot be generalized in the absence of head-to-head studies.\(^5\)

**The Next Generation of Drugs: Circumventing Resistance to Antiangiogenics and Novel Immune Checkpoint Blockers**

Nearly all patients treated with currently approved targeted drugs will eventually experience disease progression. Understanding the underlying mechanisms behind VEGF resistance is an area of ongoing research. Examples of such targets include the fibroblast growth factor receptor (FGFR), MET, and the angiopoietin and endothelin pathways. Proteins along these pathways may be involved in acquired resistance to antiangiogenic agents. Usually the novel drug, often a small molecule, has a dual mechanism of action, with the goal of targeting the resistant pathway while maintaining VEGFR inhibition. Thus far, the initial clinical experience with these agents has been encouraging, despite a few setbacks. Dovitinib, a small molecule that inhibits VEGFR and FGFR, failed to show superior efficacy compared with sorafenib in a head-to-head third-line phase III trial.\(^3\) Conversely, another similarly designed small molecule, levantinib, showed a clinically meaningful PFS versus second-line everolimus as a single agent or in combination with everolimus in a randomized phase II study.\(^6\)

MET is upregulated after VEGF inhibition in several animal models and has therefore been characterized as a possible resistance mechanism to drugs targeting angiogenesis.\(^7\) One small prospective clinical trial (N=25) showed a promising PFS of 12.9 months and a response rate of 28% with cabozantinib, a receptor tyrosine kinase inhibitor (TKI) against VEGFR and MET, in a highly pretreated RCC population.\(^8\) Cabozantinib is being compared with standard everolimus in a randomized phase III trial (METEOR) in patients with VEGFR-TKI–refractory RCC (ClinicalTrials.gov identifier: NCT01865747). A first-line Alliance for Clinical Trials in Oncology–led randomized phase II trial is comparing the efficacy of cabozantinib versus sunitinib as first-line therapy in patients with mRCC with poor- or intermediate-risk prognostic features (ClinicalTrials.gov identifier: NCT01835158).

Recently, new agents targeting the immune checkpoint programmed death-1 (PD-1) and its ligand PD-L1 are actively being investigated in many tumor types, including mRCC.\(^9\) An initial phase I study investigating nivolumab, an IgG4 antibody against PD-1, reported on 34 patients with mRCC and showed a promising median OS of 22.4 months and overall response rate (ORR[KCl]) of 29% in patients who had been heavily treated.\(^7\) High-grade treatment-related adverse events were uncommon and reversible.\(^10\) Shortly after this study, 2 larger randomized studies with nivolumab showed an ORR of approximately 20%, coupled with a median OS of 18.2 to 25.5 months, which is quite encouraging.\(^11,12\) A phase III trial of nivolumab with an OS primary end point recently finished accrual and will compare this drug with standard-of-care everolimus in more than 800 patients with mRCC previously treated with a VEGF inhibitor (ClinicalTrials.gov identifier: NCT01668784).

Another alternative to PD-1 inhibition is the more selective ligand inhibition through targeting PD-L1 with MPDL3280A. This drug was administered to 69 patients with mRCC, showing a median PFS of 24 weeks and an ORR of 15%, with responses seen in patients at poor risk and with sarcomatoid histology. Similarly to nivolumab, the drug was well tolerated.\(^13\) Studies of combination strategies with PD-1 and PD-L1 inhibitors and targeted agents are ongoing.\(^9\)
Another combination strategy involves a dual immune checkpoint blockade. One study reported on 44 patients (80% of whom had received prior systemic agents) treated with nivolumab plus ipilimumab, the latter being a CTLA-4 blocker; CTLA-4 is another distinct checkpoint on the immune cell. The median PFS was approximately 38 weeks, the ORR was 50%, and toxicity favored the combination using low-dose ipilimumab, leading to an ongoing large phase III trial with this combination (ClinicalTrials.gov identifier: NCT02231749).

Overall, the coming years have the potential to bring a new generation of systemic therapies in mRCC, with checkpoint inhibitors and novel targeted therapy based on circumventing resistance to antiangiogenic drugs. These strategies will hopefully lead to progress in achieving increased and sustained survival in mRCC and to more options for patients based on the highest level of evidence.

References