
Current Perspectives in Metastatic Renal Cell Carcinoma Treatment: The Role of Targeted Therapies

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1. Introduction

Renal cell carcinoma (RCC) accounts for approximately 3% of adult malignancies and close to 90% of all renal neoplasms. Renal cell carcinomas, by definition, are tumors that originate in the renal cortex. These tumors are often asymptomatic, have diverse clinical manifestations, and can be associated with hereditary syndromes. Surgery is the treatment of choice for localized RCC. In localized RCC, partial nephrectomy for small tumors and radical nephrectomy for larger tumors continue to be the gold standard. Surgical practice has reduced morbidity and has advanced toward more limited and less invasive resection approaches. In addition, cytoreductive nephrectomy is often indicated before embarking on systemic treatment in patients with metastatic disease.

In recent years, there has been a shift from radical nephrectomy toward more nephron-sparing approaches. RCC still remains a predominantly surgical disease because RCCs are frequently characterized as tumors that are resistant to chemotherapy and radiation. However, advances in the treatment of metastatic RCC have evolved, primarily with biologic response modifiers.

The management of RCC has undergone the most significant transformation. Scientific understanding of the molecular basis of cancer and the role of growth factors have resulted in the identification of signaling pathways relevant in the pathogenesis of renal cell carcinoma. This knowledge provided the impetus for developing new drugs that target and inhibit these different pathways. Previously, systemic therapy for renal cancer has been limited to the use of interleukin-2 and the off-label use of interferon. These drugs formulated an immunotherapeutic approach to the treatment of advanced renal cancer. Translational research and participation of patients with advanced renal cell carcinoma in clinical trials have resulted in

the approval of six systemic targeted therapies. These include sorafenib tosylate, sunitinib malate, temsirolimus, everolimus, bevacizumab in combination with interferon, and most recently, pazopanib. Each of these drugs has increased therapeutic options and appears to prolong survival for patients with advanced renal cancer.

2. Biologic basis of targeted therapy

Recent advancements in the understanding of the genetics of RCC have led to a new pathological classification of five different subtypes of RCCs: clear cell, papillary, chromophobe, collecting duct carcinoma (Bellini Duct tumor), and renal carcinoma unclassified (renal medullary carcinoma). This classification is primarily based on cytologic appearance and the cell origin in combination with growth pattern and genetic alterations [1].

The grading of RCC is based on the morphology of a neoplasm with hematoxylin and eosin (H&E) staining on microscopy. The most popular and widely used system for grading RCC is a nuclear grading system described by Fuhrman, Lasky, and Limas in 1982. This system categorizes RCC into one of four grades based on nuclear characteristics and has been shown to correlate with prognosis.

Adenocarcinomas represent the great majority (85%) of renal cell cancers. Adenocarcinomas may be subdivided into clear cell renal carcinomas, the most common form of kidney cancer; Many cases of clear cell carcinoma are linked to inactivation of the von Hippel-Lindau tumor suppressor protein (pVHL), [2]. VHL is a 213 amino acid protein that polyubiquitinates hypoxia-inducible factor 1 alpha (HIF1alpha) which marks it for destruction by the cellular proteasome. Normally, low oxygen conditions allow HIF1alpha to accumulate and bind to HIF1beta thereby creating a complex that transcriptionally activates genes. In patients with aberrant VHL, HIF1alpha is left to accumulate freely without degradation even under normal oxygen conditions and thus the transcription of genes related to glucose metabolism, apoptosis, angiogenesis and endothelial stabilization are abnormally promoted. This disordered response to hypoxia activates over 100 HIF-responsive genes which include growth factors and their receptors such as VEGF, platelet-derived growth factor (PDGF), and transforming growth factor alpha/beta (TGF), [3].

Inactivation of the VHL gene is an early step in clear cell renal carcinogenesis, at least for those tumors associated with VHL disease. Subsequent studies have shown that VHL inactivation is also common in non-hereditary clear cell renal carcinoma. Approximately 50% of sporadic clear cell renal carcinomas harbor somatic mutations affecting the maternal and paternal VHL locus.

Another downstream effect of the VEGF receptor (VEGFR) pathway is the activation of PI3 kinase and Akt which in turn promote mTOR kinase [4]. mTOR is a central component of intracellular pathways that promote tumor growth and proliferation, cellular metabolism and is a mediator of the hypoxic response as an upstream activator of HIF1alpha. When mTOR and raptor combine to form an activated complex, they phosphorylate and thus activate the

eukaryotic translation initiation factor 4E binding protein-1 (eIF-4BP1) and ribosomal S6 kinase (p70s6k). This leads to the synthesis of cellular proliferation proteins such as cyclin D1, angiogenesis mediators such as VEGF, and hypoxia response regulators such as HIF1alpha [5].

3. Targeted therapies

Systematic studies of cell lines in which pVHL or HIF status has been manipulated suggest that as many as 100 HIF-responsive genes might be dysregulated when pVHL is crippled [6]. A number of these genes encode proteins that are implicated in tumorigenesis. This makes them amenable to pharmacologic attack. Evidence now indicates that targeting these HIF-responsive genes can alter the natural history of human renal carcinoma.

Fortunately, a number of drugs have been identified that indirectly downregulate HIF protein levels. One such drug, rapamycin, inhibits mTOR, which plays a critical role in the regulation of protein translation. This in turn affects HIF α , which is very sensitive to changes in protein translation due in part to its high metabolic turnover rate. Inhibitors of mammalian target of rapamycin (mTOR) like rapamycin, downregulate HIF, [7].

4. Targeting HIF-responsive growth factors

4.1. Vascular endothelial growth factor

Clear cell renal carcinomas are notoriously angiogenic. Indeed, prior to the availability of computed tomography, renal angiograms were often used to diagnose these tumors. Renal carcinomas overproduce a variety of angiogenic moieties including vascular endothelial growth factor (VEGF), the product of a HIF-responsive gene. In addition to promoting angiogenesis, VEGF might suppress antitumor immune responses as well. It has also been suggested that VEGF has direct stimulatory effects on renal carcinoma cells, although these findings await further corroboration, [8, 9].

Several drugs that inhibit VEGF, or its kinase insert domain-containing receptor (KDR), have activity against clear cell renal carcinomas. In a randomized phase II study, patients with metastatic renal carcinoma who were treated with 10 mg/kg (but not 3 mg/kg) bevacizumab, a neutralizing antibody against VEGF, exhibited a significant delay in time-to-disease progression, [10]. Other unrelated KDR inhibitors such as SU11248 (sunitinib maleate), BAY43-9006 (sorafenib), and AG-013736 also appear to have significant activity against this tumor subtype, [11, 12].

5. VEGFR tyrosine kinase inhibitors

VEGF stimulates endothelial cell proliferation and survival. Immature blood vessels appear to be exquisitely sensitive to VEGF withdrawal. In contrast, mature blood vessels are less

sensitive to VEGF withdrawal because their endothelial cells are responsive to additional survival factors such as platelet-derived growth factor (PDGF) released from surrounding pericytes. Ongoing efforts to improve our understanding of the basic biology of RCC have identified several potential targets for therapeutic modulation. One particularly promising area of investigation is the role of VEGF in the pathogenesis of renal cell carcinoma. VEGF is a tumor-secreted cytokine that plays an important role in both normal and tumor-associated angiogenesis. VEGF exerts its biologic effect by binding to cell surface VEGF receptors, thereby inducing dimerization and autophosphorylation of intracellular receptor tyrosine kinases, leading to activation of downstream signal transduction elements. There are several forms of VEGF receptors (VEGFR), but VEGFR-2 appears to be the main receptor responsible for the proangiogenic effects of VEGF. The relevance of VEGF to tumor biology is supported by the high incidence of von Hippel-Lindau tumor suppressor gene mutations in patients with RCC, which subsequently leads to increases in VEGF expression. Receptor tyrosine kinases (RTKs) play an integral role in the signaling cascade of VEGF and PDGF [12].

RTKs have an extracellular domain that binds to their respective ligand and an intracellular domain that holds the tyrosine kinase responsible for downstream signaling. Upon ligand binding, the RTKs dimerize or multimerize to induce a conformational change that allows ATP binding resulting in autophosphorylation and transphosphorylation. These tyrosine domains are then able to phosphorylate and activate various proteins in the downstream signal transduction cascade.

6. Sunitinib

Sunitinib is an oral drug with inhibitory activity against several related protein tyrosine kinase receptors, including the platelet-derived growth factor receptor (PDGFR)- β , stem cell factor receptor (KIT), and Fms-like tyrosine kinase-3, as well as the vascular endothelial growth factor (VEGF) receptors 1, 2 and 3, [13]. Two initial phase II trials of sunitinib 50 mg/day for 4 weeks followed by 2 weeks rest in 169 metastatic renal cell carcinoma (RCC) patients who had failed previous cytokine-based therapy demonstrated an investigator-assessed objective response rate of 45%, a median duration of response of 11.9 months, and a median progression-free survival (PFS) of 8.4 months [14, 15]. Recently, a survival analysis of these patients was reported, suggesting a trend for improved median overall survival (OS) with sunitinib therapy (26.4 vs 21.8 months; hazard ratio: 0.821; 95% confidence interval: 0.673-1.001; $P = .051$). Based on these data, sunitinib has emerged as a frontline standard of care for patients with metastatic RCC. Common toxicities associated with sunitinib have included fatigue, hand-foot syndrome, diarrhea, mucositis, hypertension and hypothyroidism. Cardiotoxicity has been reported and thus monitoring may be required in patients with preexisting heart disease [16].

In a population-based retrospective analysis comparing patients treated in the IFN era ($n=131$) versus those treated in the sunitinib era ($n=69$), the patients treated with first-line sunitinib had an associated doubling in OS compared to those treated with interferon (17.3 versus 8.7 months, $p=0.004$) [17]. When adjusted for Memorial Sloan Kettering Cancer Center (MSKCC)

prognostic criteria, the HR of death for sunitinib versus IFN was 0.049 ($p=0.001$). Even those patients classified as having a poor prognosis by MSKCC criteria had a survival advantage. Current treatment algorithm for patients with met (10.7 versus 4.1 months, $p=0.0329$), suggesting that use of sunitinib is beneficial in this population as well.

7. Sorafenib

Sorafenib is an oral multikinase inhibitor that inhibits vascular endothelial growth factor (VEGF) receptors 1-3, platelet-derived growth factor receptor (PDGFR)- β , and the serine threonine kinase Raf-1 [18]. A phase III trial of sorafenib randomized 905 treatment-refractory metastatic RCC patients to sorafenib 400 mg orally twice daily or placebo [19]. In the sorafenib arm, a progression-free survival (PFS) advantage of 5.5 months vs 2.8 months was observed (hazard ratio for disease progression: 0.44; 95% confidence interval: 0.35-0.55; $P < .01$). The median overall survival was also increased for patients in the sorafenib group (19.3 vs 15.9 months) but did not reach prespecified statistical boundaries for significance. The common toxicities experienced with sorafenib are similar to sunitinib except that the hand-foot syndrome may be more pronounced and cardiotoxicity and fatigue appears to occur less frequently. Based on these data, sorafenib has been FDA approved and become a standard of care for second-line treatment of mRCC after immunotherapy failure. However, a smaller, randomized phase II of sorafenib vs interferon alfa-2b in 189 previously untreated metastatic RCC patients failed to demonstrate a PFS advantage over IFN. Compared with interferon alfa-2b, sorafenib did not significantly improve the median PFS (5.6 vs 5.7 months, respectively), [20]. Although the reason for the lack of significant effect when compared with interferon alfa-2b in the frontline setting remains unclear, one possibility is that it is because of a weaker inhibition of VEGF receptor compared with sunitinib. Although there may be patients in whom sorafenib is a preferred initial agent because of the toxicity profile or other considerations, sorafenib has largely been relegated to second-line and later therapy. The identification of those patients for whom sorafenib would be the preferred frontline treatment is needed.

8. Mammalian Target of Rapamycin (mTOR) inhibitors

Temsirolimus is an inhibitor of mammalian target of rapamycin (mTOR), a molecule implicated in multiple tumor-promoting intracellular signaling pathways.

Activation of the mTOR protein, through cellular stimuli-triggered activation of the PI3K/Akt pathway, can also result in HIF accumulation. mTOR phosphorylates and activates p70S6K, which results in enhanced translation of certain proteins, including HIF. Activated HIF translocates into the nucleus, where it triggers the transcription of a large number of hypoxia-inducible genes; among these are the growth factors vascular endothelial growth factor (VEGF) and PDGF. These growth factors interact with their respective cell-surface receptors, leading to cell migration, proliferation, and permeability. Temsirolimus and everolimus bind to the

FK506-binding protein; this resultant protein-drug complex inhibits the kinase activity of mTOR within the mTORC1 complex.

Temsirolimus was initially evaluated for patients with mRCC in a randomized phase II study of three different dose levels [21]. When patients were retrospectively stratified into MSKCC prognostic risk groups, the poor risk group appeared to have a better than expected OS, leading to further evaluation in this population.

The subsequent phase III trial with temsirolimus had a primary endpoint of OS. Six hundred and twenty-six previously untreated patients with poor prognostic criteria were randomized to temsirolimus 25mg IV weekly, IFN alpha 18 million units (MU) three times a week or temsirolimus 15 mg IV weekly plus IFN 6 MU three times a week [22]. To be considered poor risk, patients were required to have three or more of the following adverse risk features: Karnofsky performance status less than 80%, lactate dehydrogenase over 1.5 times the upper limit of normal, hemoglobin below the lower limit of normal, serum corrected calcium more than 10 mg/dl, time from first diagnosis of RCC to start of therapy of less than a year and three or more metastatic sites. Of patients included in this trial, 19% had nonclear cell or unknown histology. Temsirolimus monotherapy demonstrated an OS advantage compared to IFN alpha (10.9 months versus 7.3 months, log rank $p < 0.008$). The objective response rates were 8.6% for temsirolimus and 4.8% for IFN, which was not statistically significant. The median PFS for the temsirolimus monotherapy arm and interferon arm was 3.8 months (95% confidence interval (CI): 1.9–2.2) and 1.9 months (95% CI: 3.6–5.2), respectively. Common side effects include fatigue, hypercholesterolemia and hyperglycemia. Temsirolimus has become a first-line option for patients with metastatic RCC of any histologic subtype, appropriately applied to patients with poor prognostic criteria.

Another mTOR inhibitor, everolimus (RAD001) has recently been reported to improve progression-free survival in a phase III trial of patients with mRCC who had progressed on sunitinib, sorafenib or both [23]. These patients were randomized to receive either everolimus 10mg orally daily or placebo and were stratified by the number of previous tyrosine kinase inhibitors (TKI) and MSKCC 'previously treated' risk groups (one point each for anemia, hypercalcemia, and Karnofsky performance status < 80 ; 0 points=favorable, 1 point=intermediate, 2 +points=poor risk group). The primary endpoint was PFS and in the everolimus and placebo groups it was 4.9 months and 1.87 months ($p < 0.0001$), respectively. The PFS benefit was seen in all three MSKCC risk groups. Common side effects included asthenia, anemia and stomatitis. Up to 14% of patients experienced some form of pneumonitis. OS was 14.79 and 14.39 months ($p = 0.117$) respectively, however crossover to everolimus was permitted in this study. One hundred and six patients randomized to placebo crossed over to receive everolimus after initial progression. For this group, the median PFS was 5.09 months, which is similar to the PFS of the original everolimus group. This is the first agent tested in a second-line trial after initial TKI failure to demonstrate benefit. US FDA approval has recently been granted.

9. Axitinib (AG013736)

AG013736 is another orally bioavailable small-molecule TKI of VEGFR-2 and PDGFR-B that has shown activity in metastatic RCC. Preclinical data from Inai and colleagues suggested that AG013736 inhibited angiogenesis and caused regression of existing tumor vessels. A phase II trial enrolled 62 treatment-refractory patients with RCC that had progressed on sorafenib [24]. They were treated with oral axitinib 5mg twice daily. Of 62 patients, 13 (21%) patients exhibited a partial response and the median PFS was 7.4 months. Another phase II trial with axitinib enrolled cytokine-refractory, nephrectomized patients and demonstrated a response rate of 44.2% and a median time to progression of 15.7 months [25]. Grade 1/2 toxicity included hypertension (33%), fatigue (29%), nausea (29%), diarrhea (27%), hoarseness (19%), anorexia (17%), and weight loss (15%). Grade 3/4 toxicity included hypertension (18%), diarrhea (6%), fatigue (6%), blister (4%), and limb pain (4%). These studies confirm that AG-013736 produces a substantial objective response rate in cytokine-refractory, metastatic RCC.

10. Pazopanib (GW786034)

Pazopanib hydrochloride is an oral, angiogenesis inhibitor targeting vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and c-kit. In October 2009, the US Food and Drug Administration–approved pazopanib for the treatment of patients with advanced renal cell carcinoma. In the international, multicenter, randomized, double-blind trial, 435 patients were randomly assigned (2:1) to receive pazopanib (n = 290) or placebo (n = 145), [26]. The study demonstrated a median progression-free survival (the primary endpoint) of 9.2 months in the pazopanib arm vs 4.2 months in the placebo arm (hazard ratio [HR]: 0.46; P <.001). This effect was observed both in patients who had not received previous treatment (HR: 0.40) as well as patients pretreated with cytokine therapy (HR: 0.54). The median duration of responses was 13.5 months. The overall survival results were not mature yet and 40% of patients died by the time of final data cut-off. Based on this study, the recommended dose of pazopanib for the treatment of advanced renal cell carcinoma is 800 mg administered orally once daily without food (at least 1 hour before or 2 hours after a meal).

11. BAY 73-4506

BAY 73-4506 is an orally active, potent multikinase inhibitor targeting both tumor cell proliferation and tumor vasculature through inhibition of receptors of tyrosine kinases (VEGFR, KIT, RET, FGFR, and PDGFR) and serine/threonine kinases (RAF and p38MAPK). Previously untreated patients with predominantly clear cell RCC and measurable disease according to RECIST were enrolled in this multicenter, open-label, phase II study. Eligibility criteria included ECOG performance status 0–1, low or intermediate risk MSKCCC prognostic profiles, and adequate bone marrow and organ function. Treatment consisted of BAY 73-4506

160mg once daily on a 3 weeks on/1 week off schedule. The primary endpoint was overall response rate. Preliminary efficacy data of the 33 patients evaluable for response show a 27% partial response (PR) and a 42% stable disease (SD) rate [27].

12. Sequence of targeted therapy

Currently, we have the fortunate problem of having several agents demonstrating efficacy in the first- and second-line setting, with a number of other small molecule inhibitors that target VEGFR tyrosine kinase being evaluated in mRCC consistently showing activity. With similar mechanisms of action, clinical responses have been observed, including in patients that have previously received TKI therapy. Part of the challenge in moving forward is the lack of understanding of the biologic underpinnings of resistance to the currently approved agents and uniform clinical definitions of what truly constitutes treatment resistance.

Studies combining targeted therapies are being performed with the known caveat that combinations are associated with high financial cost and risk of increased toxicity due to additive and overlapping side effect profiles. Rational combinations of active agents continue to be evaluated. Currently, combinations of targeted therapy remain experimental and they should only be employed in the context of a clinical trial.

Targeted agents are also being studied in the adjuvant setting for patients with resected high-risk RCC. The Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma (ASSURE) intergroup trial randomizes high-risk nephrectomized patients to 1 year of sorafenib, sunitinib or placebo (estimated enrolment: 1332, primary endpoint: disease-free survival (DFS)) (NCT00326898). Other trials such as the phase III sunitinib versus placebo study for the treatment of patients at high risk of recurrent RCC (S-TRAC: estimated enrolment 236, primary endpoint: DFS) (NCT00375674) and the sorafenib versus placebo trial in patients with resected intermediate or high-risk RCC (SORCE: estimated enrolment 1656, primary endpoint: DFS) (NCT00492258) will further help elucidate the effect of these agents in the adjuvant setting.

13. Combination therapy

One of the next directions in the therapy of advanced RCC involves the combination of several targeted agents to better inhibit a single pathway at several different levels or inhibition at the same level of several pathways mediating different effects. As combinations of targeted agents undergo investigation, it will be critical for these combinations to demonstrate clinical benefit above and beyond those of sequential monotherapy with the same agents, in order to justify the added toxicity and risk. Thus, prospective data in this regard are critical, and some data have recently emerged.

Combinations of VEGF-targeting agents have undergone initial testing. Several combinations of these targeted agents were studied, including temsirolimus with either bevacizumab or sorafenib. Bevacizumab was also combined with sunitinib, and PTK787/ZK222584. These combinations have frequently demonstrated enhanced toxicity, preventing the use of the maximum single-agent doses. However, temsirolimus and bevacizumab in combination could be given at full doses of each agent without enhanced toxicity and with encouraging clinical activity.

The combination of sorafenib and bevacizumab showed preliminary evidence of antitumor activity, but the full doses of each agents were not reached due to dose-limiting toxicity related primarily to hand-foot syndrome, functional stomatitis, anorexia, and fatigue.

Additional preclinical data have described potentially favorable immunomodulation with sunitinib therapy. Such data may provide a rationale for combination strategies with immunotherapy to optimize antitumor effect.

At this point, such combinations cannot be recommended for routine use outside of a clinical trial setting. A greater understanding of the pleiotropic effects of targeted agents is needed to rationally build combinations.

14. Future directions and conclusions

Surgery is the mainstay of therapy across renal cell carcinoma stages, and surgical innovation has resulted in less invasive approaches to localized disease while preserving oncologic efficacy. Renal cell carcinoma has become a model for solid tumors in which a better understanding of biologic pathways has led to systemic therapies that have dramatically improved patient outcomes. Given the availability of multiple treatment options, each with a slightly different profile of risk and benefit, there are currently multiple options for therapy. The approach to treatment requires appreciation of the risks and benefits of each of these agents, as well as knowledge of the limitations of the current data.

The goal for every metastatic renal cell carcinoma patient upon presentation is to maximize overall therapeutic benefit, meaning delaying for as long possible a lethal burden of disease while maximizing quality of life and patient convenience.

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