

Review Article

Metastatic renal cell carcinoma: Current scenario and future trends

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Abstract

An improved understanding of the biology of renal cell carcinoma (RCC) has led to the development of a number of targeted agents, which has resulted in a paradigm shift in the management of metastatic RCC. We review the current therapeutic strategies for metastatic RCC and present a synopsis of the novel agents in use today with a discussion of the phase III trials that demonstrated their clinical benefit. The management of RCC continues to evolve. The introduction of VEGF and mTOR inhibitors has markedly expanded our drug armamentarium and improved the outcome of a disease that has always been challenging to treat. Knowledge from upcoming trials will help us utilize these drugs for maximum clinical efficacy with optimal dosing and sequencing, either individually or in combination therapy.

Key words: Mammalian target of rapamycin inhibitor; novel agents; renal cell carcinoma; tyrosine kinase inhibitor; vascular endothelial growth factor inhibitor

Introduction

Renal cell carcinomas (RCC) represent less than 3% of overall cancer incidence and mortality with annual incidence of approximately 200,000 worldwide and mortality in 100,000 cases. There has been a significant increase in the incidence of RCC over the last few decades. Although the numbers of cases in Asia are the lowest, the ratio of incidence to mortality is higher.^[1] About 20% to 30% of patients present with metastatic disease at diagnosis, and about one-third of patients undergoing nephrectomy for localized disease will develop metastases.^[2] The 5-year overall survival for patients with metastatic disease at presentation remains less than 20%. An increased understanding of tumor biology of these cancers has brought in its wake the advent of therapies targeting the molecular pathways involved in its growth and

proliferation, which has thus resulted in a paradigm shift in the treatment of metastatic RCC.

One of the first targets identified was the vascular endothelial growth factor (VEGF) mediated pathway, which is involved in angiogenesis. A number of approved drugs for RCC are VEGF inhibitors; these include bevacizumab and the tyrosine kinase inhibitors (TKI) sunitinib, sorafenib, pazopanib and more recently axitinib. These drugs also affect other signaling pathways and receptors which include *raf* kinase, platelet-derived growth-factor receptors (PDGFRs) a and b, *c-kit*, FMS-like tyrosine kinase 3 (Flt-3), and *ret* receptor tyrosine kinases. The mammalian target of rapamycin (mTOR) pathway, which regulates Hypoxia-inducible factor-1a (HIF-1a), has also been successfully targeted for therapeutic intervention and mTOR inhibitors that are currently approved for RCC include temsirolimus and everolimus. In this review, we will discuss the current strategies for management of metastatic RCC and future directions that are likely to further improve clinical outcomes.

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Cytoreductive Nephrectomy and Metastatectomy

The evidence for cytoreductive nephrectomy stems from two large phase III trials that predate the use of targeted therapies. In the Southwest Oncology Group 8949 study, 120 patients randomized to radical nephrectomy followed by therapy with interferon (IFN) alfa-2b had a median

survival of 11.1 months as compared to 8.1 months for the 121 patients treated with IFN alfa-2b alone ($P = 0.05$),^[3] independent of performance status, metastatic site, and the presence or absence of a measurable metastatic lesion. In the European Organization for Research and Treatment of Cancer 3094 study, survival of 17 months was seen in the surgery arm as compared to 7 months for IFN alone arm (hazard ratio [HR] 0.54; 95% confidence interval [CI] 0.31-0.94).^[4] The combined meta-analysis of these two trials showed that overall median survival was longer in the nephrectomy plus interferon group (13.6 vs. 7.8 months, HR 0.69) with a 31% decrease in the risk of death ($P = 0.002$) and higher 1-year overall survival in the nephrectomy plus IFN group as compared to the IFN only group (51.9% vs. 37.1%).^[5] The rationale for this benefit remains unexplained. Possible hypotheses have included reduction of tumor burden and improvement in performance status, thereby improving prognosis and enhancement of potential immune-mediated response to systemic therapy. Whether these findings are applicable in today's scenario, where there are much more efficacious drugs as compared to cytokines remains unclear. However, the majority of patients in clinical trials evaluating these therapies had undergone cytoreductive nephrectomy,^[6-10] and therefore, till further data is available, should be considered an option for selective patients. Prospective trials are exploring the role of cytoreductive nephrectomy with sunitinib and should help to resolve its clinical utility in conjunction with newer molecules.^[11] Another approach being investigated is the incorporation of a targeted agent such as sunitinib or bevacizumab in the neo-adjuvant setting followed by nephrectomy.^[12-14] Metastatectomy, especially in patients with good performance status, limited disease burden where complete excision is possible or for patients with symptomatic disease remains an acceptable intervention.

Cytokine Therapy and Other Immunotherapeutic Strategies

RCC is considered a malignancy amenable to immune manipulation. Various immune-potentiating strategies have been applied to the treatment of RCC, but till date, cytokine therapy with IFN alpha and interleukin 2 (IL-2) are the only ones that have had some degree of clinical success.

IL-2 is a strong pro-inflammatory cytokine which stimulates T-cell mediated immunity, and increases cancer directed cytotoxic T-lymphocytes and NK cells. Different schedules and modes of administration have been explored. High dose intravenous IL-2 has shown to produce durable sustained remission in a small subset of patients, albeit at a high cost and toxicity. In 7 phase II studies,^[15] a total of 255 patients received recombinant IL-2 (600,000 or 720,000 IU/kg) as

a 15-minute intravenous infusion every 8 hours for up to 14 consecutive doses over 5 days as clinically tolerated with maximal support. Complete response was seen in 17 patients (7%) and partial response in 20 patients (8%).

IFN alpha has also been investigated in a number of trials, but the response rate is at best 15%, with a short lived response (approximately 4 months) and overall survival (OS) of about 13 months,^[16,17] all at the cost of significant toxicity. An outcome of these multiple trials was the acceptance of IFN as the comparator for ongoing trials with novel agents in RCC.^[18]

Molecularly Targeted Therapy

Von Hippel-Lindau (VHL) tumor-suppressor gene inactivation is seen in familial VHL cancer syndrome and in more than 80% of sporadic RCCs.^[19] VHL protein regulates cell response to hypoxia via the HIF-1a^[20] and inactivation leads to accumulation of HIF-1a, which results in increase of pro-angiogenic factors including VEGF.^[21] The VEGF family ligands act via the vascular endothelial growth factor receptor (VEGFR) to promote cell growth, proliferation, migration, chemotaxis and increase vascular permeability and as such have a central role in cancer angiogenesis. VEGF inhibition was, therefore, investigated as a therapeutic strategy and initiated the development of several molecules, which ushered in the era of targeted therapy.

Another downstream signaling pathway that has lent itself to therapeutic application is the phosphatidylinositol-3 kinase (PI3K)/Akt/mTOR pathway. This pathway gets activated by various growth factors and is responsible for initiating a host of cellular functions including protein synthesis, glucose homeostasis, cell growth, differentiation, survival, and migration.^[22] Cell growth, proliferation, and death is governed by a multitude of complex of molecular cell signaling pathways, and it is simplistic to assume that the entire network can be affected by one molecule. Nonetheless, the success of targeted agents is proof of principle that at least temporarily RCC can be overcome.

VEGF Inhibition by Bevacizumab

Bevacizumab is a recombinant humanized monoclonal immunoglobulin G1 antibody that binds to VEGF extracellularly and prevents binding of VEGF to the VEGFR (primarily VEGFR-2), which ultimately leads to inhibition of its biologic activity.

In the AVOREN phase III trial,^[23,24] 649 newly-diagnosed RCC patients (clear cell histology) were randomized to bevacizumab (10 mg/kg intravenously every 2 weeks)

plus IFN alpha-2a (9 million units subcutaneously 3 times a week) vs. interferon alpha and placebo, until disease progression. There was no difference in OS, however, there was a significant difference in PFS between both arms, as median PFS was 10.2 months in the bevacizumab and IFN arm compared to 5.4 months in IFN plus placebo arm (HR 0.63; $P = 0.001$) and overall response rate (ORR) 31% vs. 13%, respectively ($P = 0.001$). More than half the patients in both arms received at least one other line of therapy subsequently, and this was felt to have impacted the results of the OS analysis. Similar results were seen in the Cancer and Leukemia Group B (CALGB) 90206 trial^[25] where 732 treatment-naïve RCC patients were randomized to bevacizumab plus IFN alpha-2b vs. IFN-alpha 2b alone. Here too, there was a significant difference in PFS with median PFS of 8.5 months in the bevacizumab plus IFN group vs. 5.2 months in patients belonging to the IFN alone group ($P < 0.0001$) and higher ORR as compared in the combination arm (25.5% vs. 13.1%, $P < 0.0001$). The improvement in PFS in both studies was at the cost of an additional toxicity in the bevacizumab group with increased rates of grade 3 hypertension, anorexia, fatigue, and proteinuria. The FDA approved bevacizumab in combination with IFN alpha for metastatic RCC in July 2009.

Tyrosine Kinase Inhibitors

Another approach to block the VEGF and other intracellular signaling pathways is by inhibition of the tyrosine kinase enzymes, which are responsible for the activation of signal transduction cascades, through phosphorylation of various proteins. A number of small molecule tyrosine kinase inhibitors have been used in RCC with success.

Sunitinib

Sunitinib is an oral, multi-targeted, selective tyrosine kinase inhibitor, which binds to the intra-cellular domain of VEGFR, PDGFRs a and b, Flt-3, and other *kit* receptor tyrosine kinases. In a phase III trial, 750 treatment-naïve metastatic RCC patients (clear cell histology) were randomized to sunitinib (50 mg orally once-daily for 4 weeks, followed by 2 weeks off treatment) vs. IFN alfa-2a (9 million units subcutaneously three times weekly).^[26] Median PFS was prolonged in the sunitinib arm (11 vs. 5 months; 95% CI 0.32 – 0.54; $P < .001$). This benefit was maintained in all MSKCC risk categories, (good-risk 14.5 vs. 7.9 months; intermediate-risk 10.6 vs. 3.8 months; poor-risk 3.7 vs. 1.2 months), and there was higher ORR in the sunitinib arm as compared to the IFN alpha arm (31% vs. 6%; $P < .001$). OS was also prolonged with sunitinib (26.4 months vs. 21.8 months; HR 0.82; 95% CI 0.67 – 1.00; $P = .051$). Side effects related to sunitinib therapy were

grade 3 diarrhea, vomiting, hypertension, and hand-foot syndrome. Fatigue was higher with IFN alpha, and patients on sunitinib had better quality of life ($P = < 0.0001$).

Alternate dosing schedules have been explored in an effort to mitigate the side effects associated with sunitinib therapy. In a randomized phase II study, an intermittent schedule was compared to continuous dosing (37.5 mg daily without breaks). Although there was no difference in median OS and ORR or side effects, there was a trend towards an inferior time to progression (TTP) in the continuous arm (7.1 months) as compared to the intermittent schedule (9.9 months) ($P = 0.09$).^[27]

Sorafenib

Sorafenib is another potent inhibitor of *raf* kinase, VEGFR, PDGFR-b, Flt-3, *c-kit* protein and *ret*-receptor tyrosine kinases. In the phase III TARGET trial, 903 patients with clear cell histology RCC who had failed prior standard therapy were randomized to sorafenib (400 mg orally twice-daily) vs. placebo.^[28] The PFS was prolonged for the sorafenib group as compared to placebo (5.5 vs. 2.8 months; HR 0.44, 95% CI 0.35 - 0.55), but there was no difference in OS. The most common toxicities from sorafenib were diarrhea, nausea, rash, fatigue, hand-foot syndrome, and alopecia. Sorafenib has been compared to IFN alpha as first line therapy in a small randomized phase II trial and did not show any difference in PFS.^[29] Currently, it is not the preferred TKI in the first line setting. Sorafenib was approved by the FDA in December 2005 for advanced RCC, and sunitinib was approved in January 2006.

Pazopanib

Pazopanib is another multi-targeted tyrosinase kinase inhibitor of VEGFR, PDGFR a and b and *c-kit*. In a randomized phase III trial, metastatic RCC patients (clear cell histology), who were either treatment-naïve or status-post cytokine treatment, were randomized to pazopanib (800 mg orally daily) vs. placebo. Patients on pazopanib had significantly prolonged PFS as compared to placebo (9.2 vs. 4.2 months; HR 0.46, 95% CI 0.34 to 0.62; $P = .0001$). This PFS difference in favor of pazopanib was maintained in the treatment-naïve subpopulation (11.1 vs. 2.8 months; $P = 0.0001$), and the cytokine-pretreated subpopulation (7.4 vs. 4.2 months; $P = .001$). The ORR was 30% with pazopanib compared to 3% with placebo ($P = 0.001$) with a median duration of response of over 1 year. The most frequent side effects were diarrhea, hypertension, electrolyte abnormalities, and changes in hair color, nausea, anorexia, and vomiting.^[30] Pazopanib received FDA approval in October 2009.

Axitinib

Axitinib is a second generation highly potent angiogenesis inhibitor that selectively targets VEGFR and to a lesser degree PDGFRs and *c-kit*. In a phase III trial, 723 RCC patients who had failed prior therapy were randomized to axitinib (5 mg orally twice-a-day) or sorafenib (400 mg orally twice-a-day).^[31] Patients on axitinib who did not develop hypertension had dose increments up till 10 mg twice-daily as there is some evidence to suggest that in RCC, hypertension correlates with clinical efficacy.^[32] Axitinib therapy compared to sorafenib resulted in significant improvement in PFS (6.7 vs. 4.7 months; HR 0.665, 95% CI 0.544 – 0.812; $P < 0.0001$) and higher ORR (19% vs. 9%; $P = 0.0001$). This benefit was most striking in patients who had received only prior cytokine therapy (12.1 months with axitinib compared to 6.5 months median PFS with sorafenib; $P < 0.0001$). The most frequent side effects (> 30%) associated with axitinib were diarrhea, hypertension, fatigue, decreased appetite, nausea, and dysphonia. OS results for this trial are still pending. This is the first phase III study that compared the clinical efficacy of two targeted agents head to head. On the basis of this trial, FDA approved axitinib for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy in January 2012.

Tivozanib

Tivozanib is another highly potent second generation selective small-molecule inhibitor of VEGFR. A phase II randomized trial of patients with metastatic RCC (clear cell histology) and prior nephrectomy who received tivozanib (1.5 mg once-daily for 3 weeks followed by 1 week off) vs. placebo resulted in a median PFS of 11.8 months for the tivozanib arm.^[33] A randomized phase III study comparing tivozanib with sorafenib in patients with advanced clear cell RCC and prior nephrectomy without prior VEGF treatment is ongoing.^[34]

A common theme in all the studies with VEGF inhibitors and TKI's has been the inclusion of patients with only clear cell or predominantly clear cell histology. Most of the patients in these trials (89-100%) had undergone prior nephrectomy and had good performance status, delineating the population where VEGF therapy results in maximum clinical gains.

Mammalian Target of Rapamycin (mTOR) Inhibitors

The mTOR protein is a kinase enzyme composed of two complexes - mTORC1 and mTORC2. Rapamycin and

its analogues temsirolimus and everolimus bind to an intracellular protein FK-binding protein 12 and inhibit the kinase activity of mTORC1; mTORC2 is insensitive to this group of drugs.^[35] Inhibition of mTOR results in suppression of downstream signaling and inhibition of angiogenesis.^[36]

Temsirolimus

In a phase III trial, 626 treatment-naïve RCC patients with poor-prognosis (at least 3 of 6 poor risk predictors) and all histologies were randomized to temsirolimus (25 mg intravenously every week) or IFN alpha or a combination of temsirolimus (15 mg every week) and IFN alfa.^[37] Patients in the temsirolimus alone arm had longer OS (10.9 months as compared to 7.3 months in the IFN arm and 8.4 months in the combination arm ($P = 0.008$) and PFS ($P < 0.001$) than those on IFN alone. Specific side effects with temsirolimus were rash, peripheral edema, hyperglycemia, and hyperlipidemia. This has been the only study to date in the first line setting to show a significant difference in median OS, regardless of whether the comparator arm was placebo or another drug. Temsirolimus was approved by the FDA in May 2007 for advanced RCC.

Everolimus

Everolimus is a potent oral mTOR inhibitor, which has shown efficacy in different cancer types. In a phase III trial, 416 patients with metastatic RCC, who had progressed on sunitinib, sorafenib, or both, were assigned to everolimus (10 mg once-daily) or placebo. Median PFS was significantly longer in the everolimus arm when compared with the placebo arm (4.9 vs. 1.9 months; $P < .0001$). 80% of patients in the placebo arm crossed over to everolimus, negating any survival advantage (median OS 14.8 months with everolimus vs. 14.4 months on placebo; HR 0.87, $P = 0.162$). The most common side effects with everolimus were stomatitis, rash, fatigue, and pneumonitis (8% of patients).^[38] Everolimus received FDA approval in March 2009 for treatment of patients with advanced RCC after failure of treatment with sunitinib or sorafenib.

Ongoing Trials and Future Trends

The success of molecularly targeted therapy in controlling a disease that was previously uniformly lethal is definitely encouraging. However, after a short period of clinical benefit, patients become resistant to these agents as the cancer cell learns to bypass the blocked pathway or utilizes other pathways for downstream signaling. To decrease resistance and improve outcomes, several studies are investigating a combination approach of integrating targeted therapy with cytokine therapy or two targeted therapies.

While feasible, the limitations so far have definitely been the addition of side effects.

Bevacizumab has been investigated with tyrosine kinase inhibitors and mTOR inhibitors. In a three-armed phase II study, bevacizumab plus IFN was compared to bevacizumab plus temsirolimus and sunitinib alone. The bevacizumab and IFN arm had PFS of 16.8 months compared to 8.2 months in both the other arms. In the combination arm, 41% of patients dropped out because of an excessive toxicity.^[39] The results of a phase III trial comparing the combination of bevacizumab and temsirolimus to bevacizumab plus IFN are pending.^[40] Another trial evaluated the combination of bevacizumab plus everolimus either as first line therapy or after failure with TKI (sunitinib or sorafenib). Median PFS was longer in treatment-naïve patients (9.1 months) compared to previously-treated patients (7.1 months).^[41] CALGB 90802, a phase III study investigating the combination of bevacizumab plus everolimus vs. everolimus alone, is currently enrolling patients.^[42] The results of the phase II RECORD-2 trial comparing bevacizumab plus everolimus vs. bevacizumab plus IFN should also be available this year.^[43] The BeST trial is a phase II trial investigating bevacizumab alone vs. bevacizumab with temsirolimus vs. bevacizumab with sorafenib vs. temsirolimus and sorafenib.^[44]

RECORD-3 phase II trial is investigating the efficacy and safety of first-line everolimus followed by second-line sunitinib vs. the opposite sequence in metastatic RCC.^[45] Both sunitinib and pazopanib are approved for first line therapy of metastatic RCC (clear cell histology); however, at this time, there is no clear winner. The COMPARZ trial and the PISCES trial are evaluating both these drugs in this setting.^[46,47] This should hopefully establish the drug of choice for treatment-naïve metastatic RCC. Appropriate sequencing of the targeted agents and incorporation of cytokine therapy in this sequence are also questions that will need answers in the coming years.

A number of pre-clinical and clinical studies are exploring immunotherapeutic strategies including dendritic cell vaccines, blockade of T-cell regulation using PD-1 or CTLA-4 antibody, T cell activation, etc... Another area of active research has been the development of clinical, genetic, and molecular biomarkers that could help identify a subset of patients with highest response to a given therapy. Clinical trials involving novel agents and application of biomarkers with both predictive and prognostic utility would help in appropriate utilization of resources for best clinical outcomes.

Conclusion

Significant progress has been made in the last few decades in the management of patients with metastatic RCC. The coming years will bring a host of novel agents inhibiting not only the VEGF and mTOR pathways but other therapeutic molecular targets as well. The challenge will be the identification of not just optimum dosing but also appropriate sequencing and combination of the plethora of available drugs and utilization of biomarkers for development of cost-effective treatment strategies.

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