

Renal Cell Carcinoma: Molecularly Targeted Therapy

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Renal cell carcinoma is the most common cancer of the kidney and is among the tumors that are the most resistant to systemic therapy. Until recently, long term survival of this disease when it was not confined to the kidney was dismal, with the use of drugs such as interleukin-2 resulting in a 5-year survival rate of less than 10% for patients with advanced disease. Nearly 30% of patients present with metastatic disease, and recurrence develops in approximately 40% of patients with localized tumors. Since December 2005, the Food and Drug Administration (FDA) has approved 6 novel drugs that target advanced disease. These molecularly targeted drugs, representing the next generation of anticancer agents, inhibit angiogenesis and tumor growth factors. Small molecule tyrosine kinase inhibitors are the prototype of cancer therapy in this century, causing fewer toxic effects in the normal cells and with targeted inhibition of malignant cell proliferation. These therapies have emerged from the understanding of the molecular genetics and biology of this tumor. Further elucidation of the mechanisms of action of these drugs and those in development will lead to more effective therapies and increase the understanding of the best ways to combine them. [P R Health Sci J 2011;30:73-77]

Key words: Renal cell carcinoma, Targeted therapy, Tyrosine kinase inhibitors

Renal cell carcinoma (RCC) has an incidence of 58,240 cases per year in the United States, with 13,040 deaths accounting for 3% of all malignancies (1). In Puerto Rico, there is an incidence of this cancer of 6.3 per 100,000 in males (118 yearly cases; 1.9% of all cancers) and of 3.2 per 100,000 in females (73 yearly cases; 1.5% of all cancers). Mortality is 2.8 per 100,000 males (52 yearly cases; 1.9% of all mortalities) and 1.2 per 100,000 females (28 yearly cases; 1.3% of all mortalities). From 2000 to 2004, its incidence in Puerto Rico increased to 1.7% in males and to 1.1% in females, with a mortality increase of 0.9% in both sexes (2). Its median age at diagnosis is 65 years. The rate of RCC in the United States has increased 2% per year for the past 65 years (3). It has various presentations, from an incidental finding in an abdominal CT scan or sonogram done for another purpose, to painless hematuria, flank pain, fatigue, or bone pain from metastases. Thirty percent of RCC patients have distant metastases at the time of diagnosis. Surgery is the principal treatment for localized disease and consists of radical nephrectomy or nephron-sparing surgery; metastasectomy and radical nephrectomy can potentially be done in order to remove all visible disease, even when advanced. The estimated 5-year survival rate ranges from 96% in limited disease to 23% in advanced disease (4). Tumor grade, local extent, and presence of nodal or distant metastases at diagnosis are the most important prognostic factors. Although a diagnosis by CT scan is 98% accurate in symptomatic patients, there is no cost-effective screening test at present. RCC is more common in males, smokers, obese individuals, and hypertensive patients; organic solvents have been implicated as etiologic agents (4-6).

RCCs can be divided into four different subtypes: clear cell (80%), papillary (15%), chromophobe (5%), and collecting duct carcinomas or sarcomas (1%). Cancers of the renal pelvis, such as ureter and bladder cancer, are usually transitional cell carcinomas. In the majority of tumors, there is an acquired or congenital mutation of the Von Hippel Lindau (VHL) tumor suppressor gene in the short arm of chromosome 3 (7-10).

The new paradigm of molecular targeted therapy has dramatically changed kidney cancer therapy in recent years. Until recently, long term survival of disease not confined to the kidney was dismal, with the use of drugs such as interleukin-2 resulting in a 5-year survival rate of less than 10% (11). Using novel drugs known as tyrosine kinase inhibitors controls the proliferation of malignant cells and the development of tumor angiogenesis, sparing the normal cells from potential side effects. Since December 2005, the Food and Drug Administration (FDA) has approved six drugs of this type (that is, drugs that target advanced or recurrent renal cell cancer) (Figure 1).

In this review, we discuss therapeutic options for patients with advanced, unresectable, or recurrent disease, which options involve utilizing agents that have been approved for clinical

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The authors have no conflicts of interest to disclose.

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use in the last 5 years and that target the pathophysiology of this deadly disease. Promising treatments have emerged as a result of the increased understanding of the molecular genetics and biology of these tumors. In order to aid oncologists to determine optimum therapies, we will discuss guidelines that have arisen out of past clinical trials involving multiple novel drugs. Although these medications are approved only for renal cell carcinoma, many of them have the potential to improve survival in individuals with other kinds of solid tumor or hematologic malignancy, as similar pathogenetic processes regulate other cancers.

Pathogenesis of Renal Cell Carcinoma

The pathogenesis of RCC is characterized by an inherited or sporadic mutation of the VHL gene in the short arm of chromosome 3 (deletion 3p, t(3;6) or t(3;8)). In at least 60% of these tumors, the VHL tumor suppressor gene is inactivated. The normal function of the VHL gene product (pVHL) is destroying hypoxia-inducible factors (HIFa) inside cells. HIFa expression leads to the overexpression of hypoxia-inducible genes with vascular endothelial growth factor (VEGF), platelet-derived growth factor beta (PDGF-b), and transforming growth factor alpha (TGF-a) overproduction, promoting tumor angiogenesis and proliferation (12-14). HIFa protein expression is found in 40% of clear cell RCC and correlates with higher levels of VEGF production (15). Tumor necrosis factor-alpha gene mutations have been identified in 75% of patients with advanced RCC (16). Another active pathway in the development of RCC is the mammalian target of rapamycin kinase complex (mTOR), which is a central regulator that senses changes in the availability of growth factors, nutrients, and fuel for kidney cells and promotes the translation of messenger RNA. Also, there is evidence that mTOR regulates HIF, thereby inhibiting angiogenesis (Figure 2) (8). Both sunitinib and sorafenib inhibit the VEGF and PDGF-b pathways. Temsirolimus, an analogue of sirolimus, is a tyrosine kinase that inhibits mTOR and has been shown to improve survival in patients with high-risk, advanced, or recurrent RCC (17).

Molecularly Targeted Agents

Tyrosine Kinase Inhibitors

Motzer et al compared interferon-alpha therapy with sunitinib, an oral tyrosine kinase inhibitor, in 750 patients with previously untreated, metastatic renal cell carcinoma (18). Sunitinib was given orally, 50 mg daily for 4 weeks with a 2 week rest period versus interferon alpha, subcutaneously, 9 million units, three times a week. Interferon alpha was widely used as a first line treatment of metastatic disease, having a response rate of 5-20% and a median overall survival rate of 12 months (19-21). Sunitinib maleate,

an antiangiogenic agent, showed a response rate of 42% in a pooled-analysis of phase 2 studies (22,23). The median progression-free survival rate was significantly longer in the sunitinib arm (11 months versus 5 months), corresponding to a hazard ratio of 0.42 (5% confidence interval [CI]: 0.32 to 0.54; $P < 0.001$). Patients in the sunitinib arm had a higher response rate (31% versus 6%) and reported a significantly better quality of life, with diarrhea, vomiting, fatigue, hypertension, and hand-foot syndrome as the most common side effects (17). Based on these results, the FDA approved sunitinib (brand name Sutent) in January 2006 as a first-line treatment for advanced RCC.

One month before, the FDA had approved sorafenib (brand name Nexavar) in patients with RCC in whom previous therapy (usually cytokines such as interferon alpha or interleukin-2) had failed. This was based on a phase-3 trial done by the TARGET Study Group (based in France and Europe) of oral sorafenib at 400 mg, twice a day, versus placebo in 903 patients with resistant RCC. The median progression-free survival rate was 5.5 months in the sorafenib group and 2.8 months in the placebo group (hazard ratio, 0.72; 95% CI: 0.54 to 0.94; $P = 0.02$) (24). Partial responses were obtained in 10% of the patients receiving sorafenib. Similar side effects of sunitinib (diarrhea, rash, fatigue, hand-foot syndrome) were reported.

In October 2009, pazopanib, another tyrosine kinase inhibitor, was approved by the FDA as a first-line therapy for advanced or recurrent RCC. Pazopanib at a daily dose of 800 mg, orally, may produce liver toxicity and prolongation of the QT interval (25-27).

mTOR inhibitors

Hudes and collaborators randomized 626 patients with high-risk features (hemoglobin less than 10 mg/dl, increased lactate dehydrogenase, metastases to multiple organs, low performance status, less than one year from initial diagnosis) to interferon alpha alone, temsirolimus alone, or the combination (17).

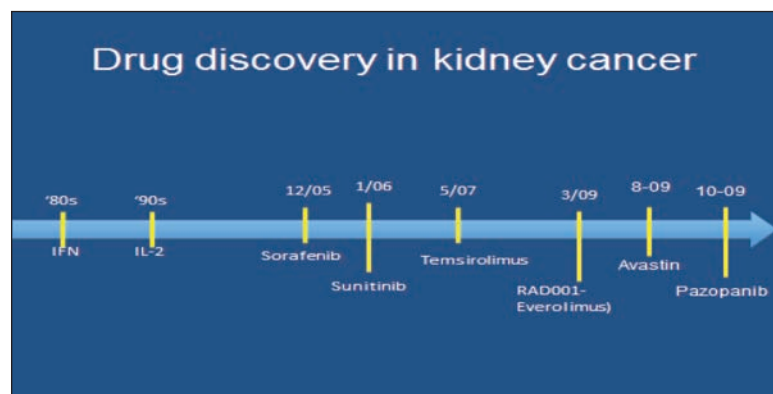


Figure 1. Dates of approval of drugs for advanced renal cell carcinoma by the Food and Drug Administration.

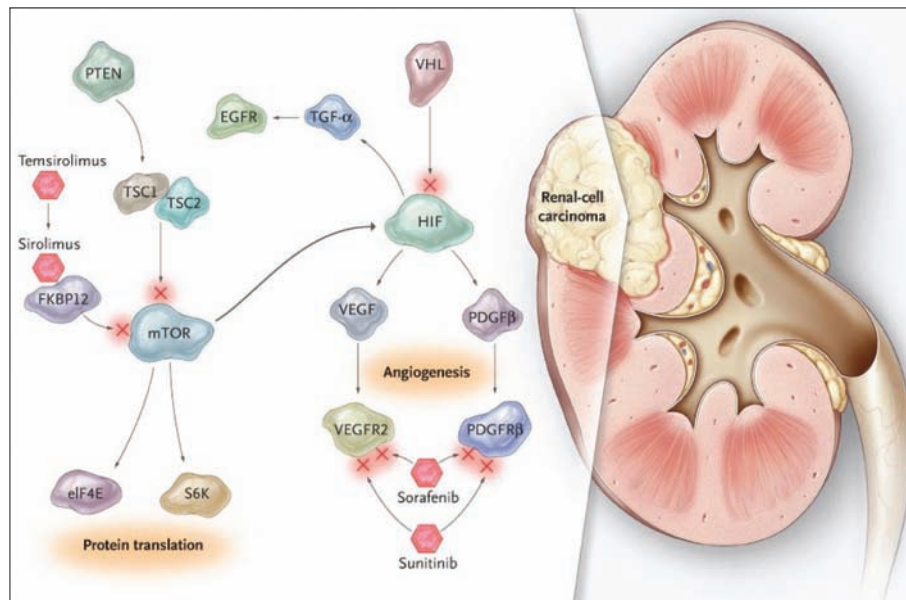


Figure 2. Molecular pathways and targeted therapies in renal cell carcinoma. VHL: Hippel-Lindau protein; HIF: hypoxia-inducible factor; TGF-α: transforming growth factor α; VEGF: vascular endothelial growth factor A; PDGFRβ: platelet-derived growth factor β; EGFR: epidermal growth factor receptor; VEGFR2: VEGF receptor 2; PDGFRβ: PDGF receptor β; PTEN: phosphatase and tensin homologue; TSC1 and TSC2: tuberous sclerosis complex 1 and 2; FKBP12: FK506-binding protein 12 kD; mTOR: mammalian target of rapamycin complex 1 kinase; eIF4E: eukaryotic translation initiation factor 4E; S6K: S6 kinase (originally published in Brugarolas J. *New England Journal of Medicine* 2007;356:186. Copyright Massachusetts Medical Society. All rights reserved).

Patients who received temsirolimus 25 mg intravenously, weekly, had a longer overall survival rate (10.9 months) than did patients receiving interferon alone (7.3 months) (hazard ratio for death, 0.73; 95% CI: 0.58 to 0.92). The most common side effects of temsirolimus were rash, peripheral edema, hyperglycemia, and hypertriglyceridemia. Temsirolimus, an inhibitor of mTOR and initially developed as an antifungal, was approved by the FDA in May 2007 as a first-line therapy for patients with advanced RCC (all histologies) and poor risk features.

Subsequently, in March 2009, everolimus, an oral mTOR inhibitor, was approved for advanced and recurrent RCC. Everolimus, which had been used as an immunosuppressant for heart and kidney transplants, was approved for second-line therapy (28).

VEGF inhibitors

Escudier and colleagues compared the effects of bevacizumab (brand name: Avastin) plus interferon-α and interferon-α alone in patients with advanced RCC (29). Median duration of progression-free survival was significantly better in the bevacizumab plus interferon-α arm compared to that which consisted of interferon-α alone (10.2 versus 5.2 months) (hazard ratio: 0.63; 95% CI: 0.52 to 0.75; $p = 0.0001$). The FDA approved this combination in August 2009 for patients with advanced RCC.

Future therapies

Newer therapies targeting other mechanisms of disease or with other VEGF or mTOR inhibitors are currently in clinical trials (30). Other inhibitors of VEGF, such as axitinib, vandetanib, vatalanib, and aflibercept (31, 32), to be used in the treatment of RCC and other tumors, are in clinical

trials. Immunotherapy, vaccine therapy, cytokines such as interleukin-7, infusions of allogeneic lymphocytes, and monoclonal antibody therapy are also under investigation (33). Multiple combinations are being tested, by such groups as the Eastern Cooperative Oncology Group, currently involved in the E2804-BEST trial, which is studying VEGF, RAF kinase, and mTOR inhibition with bevacizumab, sorafenib, and temsirolimus to treat advanced RCC (34). Also ongoing is the use of these agents at an earlier time, such as during adjuvant therapy after successful surgery but where there is a high risk of relapse. (30).

Conclusions

Treatment of RCC has dramatically changed in the past 5 years. The selection of one agent over another for therapy should take into account several issues, such as the patient's performance status, the extension of the disease, histology, the patient's preference, and drug availability. For other histologies different from clear cell carcinoma or when poor risk features are present, temsirolimus is the most used. In symptomatic patients with large tumor burdens and good to intermediate risk, sunitinib will probably be preferred due to the rapid tumor shrinkage observed with the drug (35). In asymptomatic patients or those with lung-only metastases, interferon plus bevacizumab has probably the greatest benefit. The toxicity profile of each drug and its route of administration should be discussed with each patient, and depending on the patient's choice, treatment would be better decided. An algorithm for the use of these novel targeted therapies based on the randomized trials described above is described in Table 1 (35). Carbonic anhydrase IX (CAIX), plasmatic VEGF level, hypoxia-inducible factor-2-α (HIF-2-α) expression,

phospho-S6, and phospho-AKT have been reported to be predictive markers of the efficacy of different agents and should be investigated to determine the optimal course of therapy (36, 37).

Table 1. Algorithm for the treatment of renal cell carcinoma (adapted from Escudier B et al, *Annals of Oncology* 2010;21:759-69) (33).

Histology and setting	Risk group	Standard of care	Option
Clear cell first line	Good or intermediate risk	Sunitinib Bevacizumab +IL-2 Pazopanib	Cytokines (including high dose IL-2)
	Poor risk	Temsirolimus	Sunitinib
Clear cell second line	Post cytokines	Sorafenib Pazopanib	Sunitinib
	Post-TKIs	Everolimus	
Non-clear cell histology	Not applicable	No standard of care	Temsirolimus Sunitinib Sorafenib

The development of an effective target therapy for RCC is an example of directing treatment toward both the biological characteristics and the molecular genetics of the different malignancies. This approach is under study for diverse solid and hematologic cancers, as common pathogenetic mechanisms are involved in diverse malignancies. In addition to producing longer survival rates and improving quality of life, these treatments aim to control the malignant cells, with less toxicity afflicting the normal ones. These agents probably do not specifically target the VEGF and PDGF-beta pathways, but instead act through other mechanisms. Elucidation of how these drugs inhibit tumors is the basis for new drug development and for their optimal use either as combination or sequential therapy. These discoveries will not only be of help to patients with renal cell carcinoma, but also to those with other malignancies that possess similar mechanisms of growth and progression.

Resumen

Carcinoma de célula renal es el tumor más común del riñón y es uno de los más resistentes a terapia sistémica. En el pasado, la supervivencia a esta enfermedad cuando no estaba confinada al riñón era pobre con drogas tales como interleucina-2, produciendo menos de 10% de supervivencia a los 5 años en pacientes con enfermedad metastática. Hasta un 30% de los pacientes se presentan con enfermedad metastática y se desarrolla recurrencia de la enfermedad en aproximadamente 40% de los pacientes con tumores localizados. Desde diciembre del 2005, la Administración de Drogas y Alimentos (FDA en sus siglas en inglés) ha aprobado para uso clínico seis drogas nuevas para enfermedad avanzada. Esta nueva generación de

drogas es un ejemplo de terapia molecular dirigida hacia la patofisiología de la enfermedad al inhibir angiogénesis y factores de crecimiento tumorales. Estas pequeñas moléculas inhibitorias de la cinasa de tirosina son el prototipo de la terapia contra el cáncer en este siglo, con efectos secundarios menores hacia las células normales e inhibición de la proliferación de las células malignas. Estas terapias han emergido del entendimiento de la genética molecular y biología de este tumor. Elucidar en un futuro los mecanismos de acción de estas drogas y otras en desarrollo va a permitir terapias más efectivas y ayudará en conocer la mejor forma de poderlas combinar.

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