Urology Journal
UNRC/IUA

Vol. 3, No. 1, 1-14 Winter 2006
Printed in IRAN

Review Articles

Current Management of Renal Cell Carcinoma and Targeted Therapy

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ABSTRACT

Introduction: The aim of this review is to provide an update on the current management of renal cell carcinoma (RCC) and targeted molecular therapy for metastatic RCC.

Materials and Methods: A Pubmed database search was performed using the keywords "renal cell carcinoma, treatment, management, localized disease, metastatic disease and targeted therapy" covering 1995 to 2006. The most recent articles published having clinical relevance were reviewed for the preparation of this paper.

Results: Surgery is considered as the only curative treatment for localized RCC. Currently, open radical nephrectomy is mainly performed in patients with large tumor size, locally advanced tumors and tumor thrombus extending into the vena cava. Nephron sparing surgery (NSS) is the most commonly performed procedure with excellent local cancer control in small, resectable renal tumors. Increasingly, laparoscopy is being performed and now recommended for early-stage RCCs unsuitable for NSS. Laparoscopic radical nephrectomy seems to be providing long-term cancer control comparable to open radical nephrectomy. Laparoscopic NSS is now available particularly in patients with a relatively small and peripheral renal tumor. The current therapy for metastatic RCC is inadequate and surgery is an important component of the treatment with combined immunotherapy in which response rates remain at about 15% to 25%. In the past several years, significant advances in the underlying biological mechanisms of RCC development have permitted the design of new molecularly targeted therapeutics such as antibodies, tumor vaccines, anti-angiogenesis agents and small molecule tyrosine kinase inhibitors in order to improve treatment options.

Conclusion: Surgery is the only curative treatment for localized RCC and NSS cures most of the patients with early-stage disease. Currently laparoscopy is recommended for early-stage RCCs unsuitable for NSS. Better understanding of the molecular pathways of carcinogenesis in RCC leads to the discovery of new drugs which can prolong survival in metastatic RCC.

KEY WORDS: renal cell carcinoma, treatment, management, localized disease, metastatic disease, targeted therapy

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Introduction

Renal cell carcinoma (RCC) accounts for 3% of adult solid tumors, and each year more than 30000 new cases in the United States and 20000 in the European Union are detected. The highest

incidence of RCC is detected between 50 and 70 years of age and men are affected twice as often as women.[1] Due to the widespread use of imaging modalities such as ultrasonography and computed tomography, most kidney tumors are being detected incidentally with a smaller size, leading to the increased incidence of RCC.[2]

In the pathogenesis of conventional RCC, mutations leading to inactivation of the von Hippel-Lindau tumor suppressor gene (*VHL*) have been detected in the hereditary and up to 80% of sporadic forms of clear cell RCC, and premalignant lesions in the kidney such as renal intra-epithelial neoplasms have been described which seem to be sharing similar genetical changes with RCC.[3,4] There are limited independent predictors of survival in patients with RCC. Although there are promising clinical, histological, molecular, and cytogenetic parameters, none of them has yet been shown to have an independent prognostic value. Tumor stage, tumor grade, and patient performance status are the currently known prognostic indicators.[5] Presence of necrosis is also considered as a prognostic marker for RCC and has been recommended to be routinely reported and used in clinical assessments.[6]

Diagnosis, staging, and treatment of patients with RCC have improved significantly during the last 2 decades; however, despite advances in biological and immune-based therapies, response rates for patients with metastatic RCC remain at about 15% to 25%.[7] The number of patients who will benefit from cytokine-based therapy with interleukin-2 (IL-2) and/or interferon alfa (IFN-alpha) is limited, and currently, there is no proven effective therapy in patients who do not respond or relapse after this treatment. Therefore, treatment alternatives other than cytokine-based therapy are being developed in order to improve treatment options in the management of metastatic RCC, particularly in those who are unable to tolerate or who are resistant to systemic immunotherapy.

Treatment of Localized Disease

Open Surgery

Open radical nephrectomy. Radical nephrectomy (RN) cures most of the patients with localized early-stage disease,[8] but half of the patients with localized disease progress after RN.[1] Currently, open RN is mainly performed in patients with a large tumor which is not amenable to nephron sparing surgery (NSS) and can not be dealt with laparoscopy, in the presence of complicated tumor thrombus extension into the vena cava and when there is need for surgery for other diseases (eg, renal artery stenosis) or single organ metastases when metastasectomy is being performed. Due to the low incidence of unsuspected lymph nodes and the rarity of the lymph node involvement without distant metastases, lymph node sampling is currently recommended in case of suspicion. Adrenalectomy seems to be unnecessary unless there is involvement on imaging studies or at the time of operation and in tumors not involving the upper pole. The 5-year patient survival rates have been reported to be 75% to 95% for organ-confined disease, 65% to 80% for perinephric fat or adrenal involvement, 40% to 60% for vena cava thrombus, 10% to 20% for lymph node involvement, and 0% to 5% for metastatic disease after RN.[9]

Open partial nephrectomy. Although RN was the standard treatment of kidney tumors in the past,[10] recently, due to similar cancer-specific survival rates detected for patients undergoing RN or NSS for small kidney masses (< 4 cm), NSS is considered as the treatment of choice in most kidney tumors.[11-13] Because of the increased prevalence of incidentally detected RCCs with smaller sizes, NSS is increasingly being performed with a successful cancer control and preservation of the renal parenchyma. The tumor(s) has to be removed very carefully with a minimal safety margin, and in case of doubt, ultrasonography or biopsy of the tumor bed may be used.[14] Wedge resection and polar nephrectomy are the surgical techniques of choice. Water-jet resection is a recently developed technique that holds some promise. Although tumor enucleation might be associated with an increased risk of positive surgical margin,[15] some authors suggest enucleation as a less-invasive alternative to ordinary NSS for small RCCs by using microwave tissue coagulation or laser for the tumor and tumor bed.[16]

The disease-free survival has been detected to be decreased in patients undergoing NSS for lesions larger than 4 cm compared to those with a tumor smaller than 4 cm and those who undergo RN; therefore, NSS is recommended for peripherally located tumors smaller than 4 cm in size (Table 1).[17] Recently, no significant differences in cancer specific survival and distant

TABLE 1. *Disease-free survival rates in 3 groups of patients with partial nephrectomy according to the tumor size*

		Five-year disease free survival (%)			
	Number of patients	Tumor < 4 cm	Tumor 4 cm to 7 cm	Tumor > 7 cm	Elective surgery (%)
Lee and colleagues[19]	79	95	-	-	47
Hafez and colleagues[16]	485	96	86	-	9
Belldegrun and colleagues[20]	108	100	90	66	58
Lerner and colleagues[17]	54	91	-	-	100

metastases-free survival were detected between patients with 4- to 7-cm RCCs treated by NSS and RN. Thus, NSS is recommended for 4-cm to 7-cm RCCs, because it results in an excellent outcome in appropriately selected patients.[18] There is controversy regarding the cutoff size of the kidney tumors for elective NSS and kidney tumors smaller than 7 cm have been considered suitable only in carefully selected patients.[13] The reported local recurrence after elective NSS is as low as 1% which demonstrated that NSS can be cured with an excellent local control.[19]

Indications for open partial nephrectomy (PN) are summarized on Table 2. Tumor size, location, surgical margin, multifocality, and pathologic variables affect the outcome in elective NSS.[13,18] Increased tumor size, pT2 or higher stages, presence of vascular invasion, and papillary or mixed histology are associated with an increased risk of multifocality.[15] Lower tumor stages, lower nuclear grades, papillary or chromophobe histology, and incidentally detected tumors are considered as good prognostic pathologic factors after PN.[18] Currently, NSS is considered as the most commonly performed procedure in the management of kidney tumors, particularly with smaller sizes which are frequently diagnosed incidentally.

TABLE 2. *Indications for open partial nephrectomy[13]*

Absolute
Tumors in a solitary kidney
Bilateral synchronous kidney tumors
Severe renal insufficiency
Relative
Presence of a pre-existing kidney disease in the contralateral side
Nephrolithiasis
Recurrent pyelonephritis
Mild to moderate renal insufficiency
Ureteropelvic junction obstruction
Vesicoureteral reflux
Presence of diseases predisposing to renal insufficiency
Diabetes mellitus
Hypertension
Presence of a known multifocal disease or underlying genetic syndromes
Papillary renal cell carcinoma
Von Hippel-Lindau disease
Elective
Kidney tumors smaller than 4 cm
Peripherally located lesions in the kidney
Healthy young individuals

Minimally Invasive Surgery

Laparoscopic radical nephrectomy. Laparoscopy has gained popularity in the management of urologic malignancies and RN can be safely performed for RCC by laparoscopy or retroperitoneoscopy leading to a less morbidity and a better patient acceptance. Laparoscopic RN (LRN) is now considered as the treatment of choice for early-stage (T1N0M0) RCCs unsuitable for NSS (Table 3).[21,22] The advantages of LRN are reduced blood loss, decreased postoperative pain, earlier recovery, decreased total time of convalescence, and decreased length of hospital stay, whereas, the cost and the need for a highly skilled operating team are the major limitations.[22] A 5-year recurrence-free survival of 91% and a 5-year cancer-specific survival of 98% have been reported for LRN, which is comparable to open RN in terms of providing long-term cancer control. Similar complication

Table 3. *The expanding indications for laparoscopic radical nephrectomy in selected patients*[20]

Larger tumors (> 7 cm, pT2)
Level 1 renal vein tumor thrombus
Cytoreductive nephrectomy
Limited locally invasive tumors into psoas or diaphragm muscle
Concomitant lymphadenectomy for small volume disease
Morbid obesity with renal cell carcinoma
Laparoscopic approach in the previously operated abdomen

rates for open RN, hand-assisted RN, and LRN have been detected (10%, 17%, and 12%, respectively), and currently laparoscopic approach is recommended for the majority of patients with stage T1 and stage T2 tumors.[23]

Laparoscopic partial nephrectomy. Laparoscopy is a minimally invasive approach which is emerging as an effective surgical alternative to open surgery for small and peripheral kidney tumors. Laparoscopic partial nephrectomy (LPN) is suggested for kidney tumors particularly smaller than 4 cm which offers advantages similar to LRN, such as earlier hospital discharge, more rapid convalescence, reduced postoperative narcotic use, and effective cancer control with acceptable complication rates (Table 4).[20, 24-26]

Ablative treatments. Ablative techniques for the treatment of RCC are an extension of NSS and include minimally invasive treatments such as cryoablation, radiofrequency ablation (RFA), and high-intensity focused ultrasonography (HIFU) which have been introduced recently. These might decrease morbidity by treating kidney tumors in situ rather than extirpation. Cryosurgery is the most studied of the ablative approaches, and clinical studies have demonstrated promising short-term results and a remarkable safety profile. Long-term studies, however, are needed in order to determine the appropriate selection criteria and to confirm a response as durable as that for PN and RN. They might have advantages compared with conventional open kidney surgery such as shorter convalescence, improved cosmetic results, reduced postoperative pain, and kidney preservation.[27]

Treatment of Metastatic Disease

Surgery and Immunochemotherapy

Renal cell carcinoma is resistant to chemotherapeutic agents due to the presence of multidrug resistance-1 gene and one-third of patients with RCC present with metastatic disease.[1,28] The current best therapy for metastatic RCC is inadequate and surgery is an important component of the treatment due to the potential for improving the effectiveness of adjuvant therapy and possibly stimulating regression of metastases with combined immunochemotherapy using IFN-alpha, IL-2, and 5-fluorouracil (5-FU).[28] Nephrectomy in metastatic RCC should be recommended to those patients with a good performance status before immunotherapy.[29] On the other hand, initial

Table 4. *Comparison of laparoscopic versus open nephron-sparing surgery (NSS) in patients with a solitary kidney tumor of 7 cm or smaller in size in a study by Gill and colleagues*[25]*

Major intra-operative complications	5%	0%	0.02
Renal/urological complications	11%	2%	0.01
Median operative time (hours)	3	3.9	< 0.001
Blood loss (mL)	125	250	< 0.001
Mean warm ischemia time (minutes)	27.8	7.5	< 0.001
Median analgesic requirement (morphine sulfate equivalents, mg)	20.2	252.5	< 0.001
Hospital stay (days)	2	5	< 0.001
Median convalescence (weeks)	4	6	< 0.001
Median preoperative serum creatinine level (mg/dL)	1.0	1.0	0.52
Median postoperative serum creatinine level (mg/dL)	1.1	1.2	0.65

*No significant differences in the overall postoperative complications were detected between two groups.

treatment with immunotherapy and delayed adjuvant nephrectomy has been proposed to avoid the morbidity of nephrectomy only in those who respond.[28]

Distinct genetic abnormalities affecting different molecular pathways result in the development of RCC leading to different clinical courses that respond differently to therapy.[30] Determination of the molecular profile of each tumor might improve treatment and guide patient selection for targeted therapies. Recently, a wide range of new agents are being introduced in the treatment of metastatic RCC.

Recently, promising response to a combination of 13-*cis*-retinoic acid with IFN-alpha-2a has been detected in patients with progressive metastatic RCC by the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Group.[31] New drugs such as gemcitabine, capecitabine, or taxane-based chemotherapeutics may show promising antitumor activity in combination with targeted therapy.[32-34] Current research is being focused on identification of novel agents and treatment modalities with a better antitumor activity such as antibodies, tumor vaccines, anti-angiogenesis agents, small molecule inhibitors, virus mediated gene transfer, and some other drugs.

The Hypoxia-inducible Pathway and RCC

The hypoxia-inducible pathway is important in angiogenesis, pH control, glucose metabolism, invasion/metastasis, and epithelial proliferation of malignant cells (Figure 1); therefore, it might play a role in the adaptation of cancer cells to a hypoxic environment and their resistance to radiation and chemotherapy.[35,36]

The *VHL* gene encodes VHL protein (pVHL) and in normoxia and a normal *VHL* gene function, pVHL targets hypoxia-inducible factor (HIF) for proteolysis.[37,38] Hypoxia-inducible factor is composed of HIF-1α, HIF-2α, HIF-3α, and HIF-1β. Although HIF-1β is constitutively expressed, biosynthesis and posttranslation of HIF-1α is regulated. Biosynthesis of HIF-1α is induced by several growth factors such as insulin-like growth factor-I (IGF-I), IGF-II, and epidermal growth factor (EGF).[39] Hypoxia controls HIF-1α at the posttranslational level via pVHL.[37] Under normoxic conditions, the HIF-α subunit is hydroxylated at 2 proline residues by an oxygen-

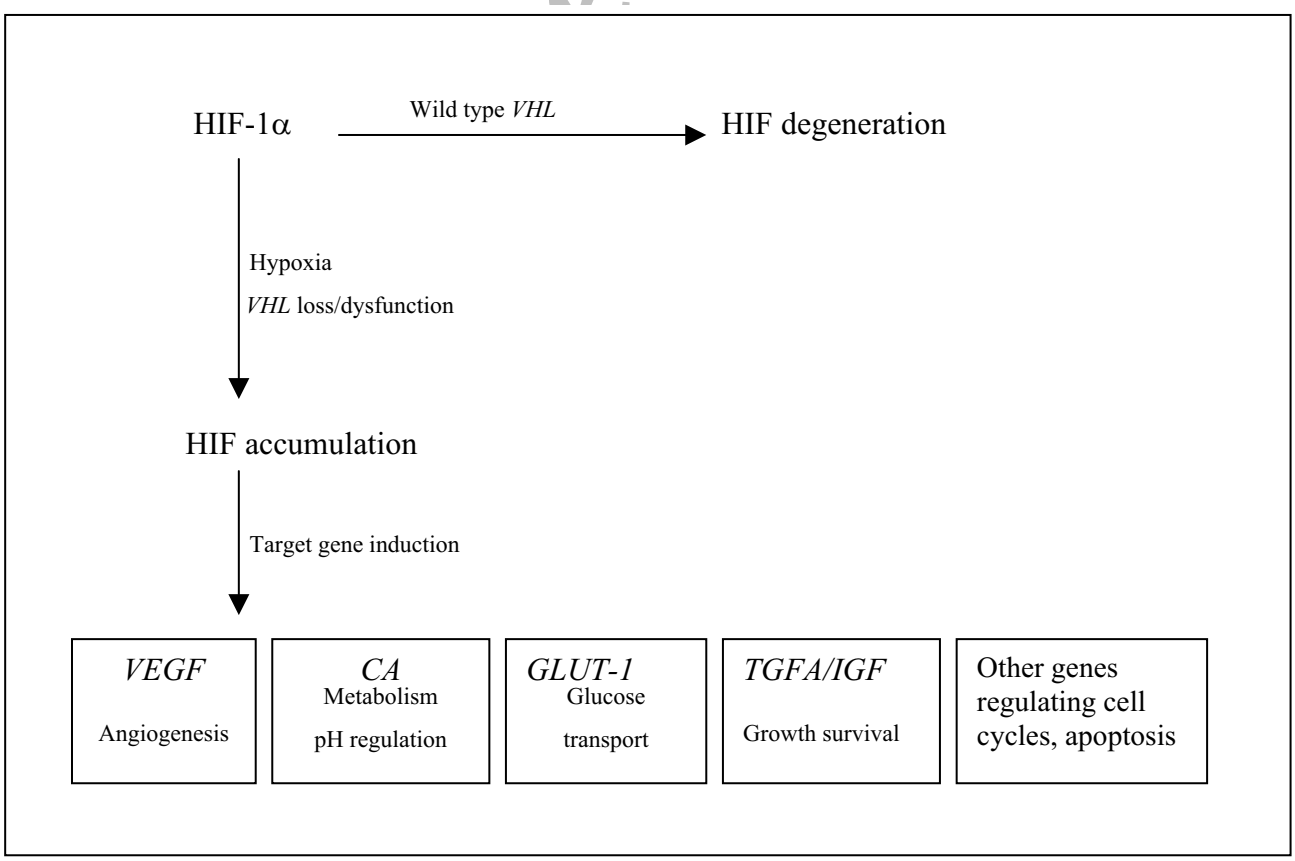

Fig. 1. The Hypoxia Inducible Pathway[30]
HIF-1: Hypoxia inducible factor-1, *VHL*: Von Hippel-Lindau gene, *TGFA*: Transforming growth factor-α, *IGF*: Insulin-like growth factor

TABLE 5. *Activation of genes and their products due to HIF-1α accumulation*[36,44,45]

Genes encoding growth and angiogenic factors
Vascular endothelial growth factor (*VEGF*)
Erythropoietin (*EPO*)
Platelet-derived growth factor (*PDGF*)
Transforming growth factor-α (*TGFA*) and its receptor
Epidermal growth factor receptor (*EGFR*)
Genes encoding enzymes involved in glucose uptake and metabolism
Glucose transporter 1 (*GLUT-1*)
Phosphoglycerate kinase (*PGK*)
pH regulation
Carbonic anhydrase IX (*CA9*)
Tissue-matrix metabolism
Matrix metalloproteinases

dependent mechanism. However, in hypoxia or defective pVHL function, due to the dysfunctional interaction between pVHL and HIF-1α, HIF-1α is not degraded and moves into the nucleus, dimerizes with HIF-1β, and activates expression of hypoxia-inducible genes (Table 5).[42,43] Defective ubiquitination of HIF subunits also occurs due to mutation, deletion, or hypermethylation of the *VHL* gene.[37,44] Mutations leading to inactivation of the *VHL* have been detected in the hereditary and sporadic forms of clear cell RCC.[45]

Loss or mutation of the *VHL* is detected in 50% to 80% of sporadic clear cell RCCs which suggests VHL-HIF tumorigenic pathway for clear cell RCC.[40,41,44–46] Therefore, *VHL* inactivation seems to cause vascular endothelial growth factor (*VEGF*) overexpression, thus leading to tumor angiogenesis in the majority of clear cell RCCs. Molecular therapeutic approaches targeting *VHL* gene pathway and genes regulated by HIF such as *VEGF*, platelet-derived growth factor (*PDGF*), or the transforming growth factor-α/epidermal growth factor receptor (*TGFA/EGFR*) autocrine loop are potential approaches in the treatment of RCC.[47]

Role of Carbonic Anhydrase IX in RCC

Carbonic anhydrase IX (*CA9*) is one of the genes that is regulated by HIF-1.[48] The *VHL* gene dysfunction can lead to the accumulation of HIF-1α and increased *CA9* expression.[49] The *CA9* gene is important in regulating intracellular and extracellular pH. Therefore, it may be important for the accommodation of tumors to an acidic and hypoxic environment leading them to further proliferate and metastasize.

It has been shown that normal fetal or adult kidney specimens do not express *CA9*, which suggests that it might be a product of tumor biology.[50] Because *CA9* is highly expressed by RCC, it might be used for vaccine development and as a target for immunotherapy.[50] Low *CA9* staining was found to be an independent prognostic factor of poor survival in patients with metastatic RCC, and complete response to IL-2 immunotherapy has been detected to correlate with high *CA9* expression.[51]

Targeted Therapy

Antibodies. The antibodies selectively interact with the antigens expressed on malignant cells; therefore, guiding toxic substances or radionuclides to the tumor might have therapeutic effects (Table 6).

G250 (WX-G250) is a chimeric monoclonal antibody developed for RCC for both therapeutic and diagnostic purposes.[6] Bleumer and colleagues administered intravenous G250 weekly to 36 patients with a metastatic RCC which was safe and well tolerated. Eleven patients achieved stable disease including 1 complete response and 1 partial regression.[52]

Bevacizumab (Avastin) is a recombinant human monoclonal antibody developed against VEGF which binds and neutralizes all biologically active isoforms of VEGF targeting the VHL/HIF/VEGF pathway.[53] Yang and coworkers administered bevacizumab to 116 patients with a metastatic RCC. Significant prolongation of time-to-progression was detected in patients receiving high-dose antibody versus placebo although survival was not significantly different.[54] No life-threatening toxicities or deaths were detected. Hypertension and asymptomatic proteinuria were detected particularly in patients who received high-dose bevacizumab antibody. All toxicities were reversible with cessation of therapy.

VEGF-trap is a combination of VEGF receptor-1 immunoglobulin (Ig) domain 2 and VEGF receptor-2 Ig domain 3 fused to human IgG1 which binds VEGF with a 100-fold greater affinity

Table 6. *Current strategies for metastatic renal cell carcinoma treatment*

Agent class	Mechanism of action/Molecular target
Antibodies	
WX-250	Targets *CA9*
Bevacizumab	Targets VEGF
Panitumumab, ABX-EGF	Targets EGFR
Cetuximab, IMC-C225	Targets EGFR
MDX-010	Targets CTLA-4 to block lymphocyte activity suppression
Anti-angiogenesis agents	
Thalidomide	Immunomodulatory agent, inhibits VEGF + bFGF
Thalidomide analogues (CC5013)	Similar to thalidomide
Endothelin-1 receptor antagonists (atrasentan, ABT-627)	Selective endothelin-1 receptor antagonist
Indolinone (SU-011248)	Inhibits VEGFR, PDGFR + FLT3 signal transduction + *c-KIT* tyrosine kinase
VEGFR + EGFR inhibitors (ZD 6474)	Targets VEGFR and EGFR
VEGFR inhibitors (PTK 787)	Selectively targets VEGFR 1, VEGFR-2 + VEGFR-3 tyrosine kinases
Thrombospondin-1 mimetics (ABT-510)	Synthetic peptide that mimics thrombospondin-1 antiangiogenic activity
Small molecule inhibitors	
Rapamycin + rapamycin analogues CCI-779, RAD001	Inhibits PI3K-AKT-mTOR signal transduction pathway
Raf kinase inhibitors	
BAY 43-9006	Targets Raf kinase + VEGFR-2
Proteasome inhibitors	
Bortezomib, PS-341	Inhibits 26S proteasome catalytic activity, prevents proteolysis
EGFR tyrosine kinase inhibitors	
Gefitinib, ZD1839 Erlotinib, OSI 774	Inhibits EGFR tyrosine kinase
Tumor vaccines	
DCs	Potent antigen presenting cells that can be pulsed or gene modified with tumor antigens such as *CA9*, tumor lysate, RNA, mutated VHL peptides, etc
HSPPC-96	Activates T cells, induces innate immune response + induces DC maturation

CA9: Carbonic anhydrase IX, VEGF: Vascular endothelial growth factor, EGFR: Epidermal growth factor receptor, CTLA-4: Cytotoxic T-lymphocyte associated-4, bFGF: Basic fibroblast growth factor
PDGFR: Platelet derived growth factor receptor, FLT3: fms-like tyrosine kinase 3, PI3K-AKT-mTOR: phosphatidylinositol 4,5-bisphosphate-AKT-mTOR, DCs: Dendritic cells, HSPPC-96: Heat shock protein peptide complex 96

than bevacizumab.[55] In a phase 1 study VEGF-trap was administered to 9 patients with metastatic RCC and no objective responses were observed. Drug-related grade 3 adverse events included hypertension and proteinuria.[56]

Erlotinib is a small-molecule EGFR inhibitor and in a clinical trial conducted in patients with a metastatic RCC, intravenous bevacizumab (10 mg/kg, every 2 weeks) was administered with oral erlotinib (150 mg, daily); a 25% partial response rate was reported.[57]

The *EGFR* is expressed up to 85% in RCC,

correlated with an aggressive disease.[58] Cetuximab (Erbituxe) and ABX-EGF (Fremont) target the EGFR. Cetuximab (C225) and Gefitinib (Iressa, ZD1839) are EGFR tyrosine kinase inhibitors. Gefitinib is recently approved by the Food and Drug Administration (FDA) for locally advanced or metastatic non–small-cell lung cancer. Although *EGF* expression is common in RCC, these agents have shown no activity.[6] In a phase 2 trial including patients with a metastatic disease, 2 of 31 patients who had failed or were unable to receive IL-2/IFN-alpha achieved objective responses and 58% had minor responses or stable disease to ABX-EGF therapy.[59] Anti-CTLA-4 (MDX-010) antibodies augment the immune system by blocking the suppression of lymphocytic activity.[6]

Tumor vaccines. It has been demonstrated that *CA9*-derived CD8+ and CD4+ T-cell epitopes can induce *CA9*-specific T cells in vitro.[50] Both primary and metastatic RCC deposits can be targeted by monoclonal antibodies (mAb) against *CA9*.[6] The *CA9*-transduced peripheral blood monocytes have been shown to generate cytotoxic T cell lymphocytes which lyse *CA9* expressing kidney cancer cells.[60] Vaccines based on *CA9*, such as granulocyte macrophage colony-stimulating factor and *CA9* (GMCA9) fusion protein vaccine are being developed in order to increase the immunogenicity of *CA9* (Table 6).[48]

A combination of radioisotopes with antibodies directed against *CA9* (sodium iodine I 131-mG250) in order to target RCC lesions are also being developed.[61] Imaging of lesions greater than 2 cm were successfully detected in early phase 2/3 clinical trials and there was an apparent improvement in survival compared to historical trials.[62]

Several tumor cell-based and dendritic cell (DC)-based vaccines for RCC are currently in clinical trials.[6] Heat shock proteins (HSPs) are known to induce DC activation and the significance of HSPs and their expression in RCC has been evaluated recently.[63] The HSP-peptide complex-96 (HSPPC-96) is currently in phase 3 trials.[64] Assikis and colleagues administered HSPPC-96 vaccine to 61 patients. Response to the treatment was seen in 21 patients and no significant toxicity was observed.[64] Of 16 patients whose disease progressed while on vaccine, 7 achieved disease stability after adding IL-2. The median progression-free survival was 18 weeks for all patients who received the vaccine, and 25 weeks for patients who also received IL-2.

Anti-angiogenesis agents. Vascular endothelial growth factor is the most potent proangiogenic tumor-secreted cytokine with critical importance in both normal and tumor-associated angiogenesis. Cytokines, growth factors, hormones, hypoxia, and tumor suppressor genes regulate the expression of *VEGF*.[65] Inactivation of the *VHL* gene leads to the increased expression of *VEGF* which is detected in the majority of RCCs.[65] Vascular endothelial growth factor receptors have been identified not only on endothelial cells, but also on the surface of kidney neoplasm cells which suggests that VEGF might stimulate tumor growth.[65] Therefore, targeting VEGF is a logical therapeutic alternative in RCC (Table 6).

Thalidomide is known as a potent angiogenesis inhibitor and inhibits endothelial cell proliferation via reducing mRNA and protein expression of basic fibroblast growth factor (bFGF) and VEGF.[65] It also reduces tumor necrosis factor-a production from macrophages, induces G1 cell cycle arrest/apoptosis, and modulates natural killer and T-cell activity; therefore, it has both antiangiogenetic and antitumor effects.[65] Low-dose and high-dose thalidomide have been evaluated as a single agent therapy in metastatic RCC. In a study on its low dose, 18 patients with metastatic RCC were administered oral thalidomide (100 mg/d), which was well tolerated.[66] Three patients (17%) achieved partial responses and 3 (17%) had a stable disease for at least 3 months after a median follow-up of 36 months.[66] In a study on high-dose thalidomide, 25 patients with a metastatic RCC were titrated to a planned dosage of 600 mg per day.[67] Although 60% of patients were not able to reach the target dose due to toxicity (lethargy, constipation, and neuropathy), thalidomide (400 mg/d) was well tolerated. After a median follow-up of 20 months, 2 out of 22 patients (9%) who could be evaluated had partial responses and 12 (55%) had a stable disease. The median survival in these two studies was 9 months. Daliani and associates investigated the efficacy of thalidomide in 20 metastatic RCC patients with disease progression after immunotherapy.[68] Eighteen patients (90%) achieved the 1200-mg target dose. Peripheral neuropathy, grade 3/4 deep vein thrombosis, and pulmonary embolism were the complications. A partial response was seen in 2 out of 19 patients

(11%) who were evaluated after 7 and 11 months of therapy, with responses lasting for 16 and 31 months. A stable disease was detected in 9 patients (47%) lasting for a median of 14 months. All patients progressed eventually and the median progression-free survival was 4.6 months. The median survival was 18.1 months. Motzer and coworkers administered thalidomide to 26 patients with a metastatic RCC.[69] Thalidomide was started at a dosage of 200 mg per day and titrated to a planned dosage of 800 mg. Sixty-nine percent of the patients received thalidomide, 400 mg or 600 mg, and due to the toxicity (grade 3 dyspnea and neurologic toxicity), only 19% were able to receive a dose of 800 mg. Although 16 patients (64%) had a stable disease, none of the 25 patients with a complete evaluation had partial responses. The progression-free survival at 6 months was 32%, and 57% of patients were alive at 1 year.

A combination of thalidomide and standard cytokine therapy has also been investigated. Thalidomide (300 mg/d) and low-dose interferon (1.2 million International Units [MIU], 3 times per day) were administered to 30 patients with untreated, metastatic RCC.[70] Six cases of partial response and no complete response were observed in the patients. Subcutaneous IL-2 (9.0 MU/m^2, days 1 through 5, weekly) and thalidomide (100 mg/d) were administered to 31 patients in a phase 1 study and 2 objective responses (6.5%) were detected.[71] Amato and colleagues administered a combination of low-dose thalidomide and IFN-alpha to patients with a metastatic RCC in a phase 2 study. Of the 14 patients evaluated, 3 (21.4%) achieved a partial response and 7 (50%) obtained a stable disease. The overall nonprogression rate was 71.4% and the overall survival was 17.4 months.[72] The combination of IL-2 and thalidomide has also been evaluated in another phase 2 study[73]; of 36 patients evaluated, there was 1 patient with a complete response, 14 with a partial response, and 11 who achieved a stable disease. The treatment was well tolerated. In a phase 1/2 trial including 8 patients, thalidomide was combined with 5-FU, IFN-alpha, and IL-2. The overall response rate was 14% and the mean time to progression was 161 days. One patient achieved radiographically complete response of the bone and pulmonary lesions.[74]

The new immunomodulatory analogs of thalidomide have also been studied in metastatic RCC. AE-941 (Neovastat) is produced from shark cartilage, and like thalidomide, it has antiangiogenic effects. AE-941 inhibits endothelial cell migration, vasculogenesis, vascular permeability (via competitive binding with VEGF receptor-2), and matrix metalloproteinases.[75] Batist and colleagues evaluated AE-941 in patients with a refractory RCC, and the median survival of 14 patients treated with high-dose AE-941 (Neovastat) was detected to be significantly longer than that in 8 patients treated with its low doses (14.4 months versus 7.1 months), and the therapy was well tolerated.[76] However, the study was not randomized and the number of patients was too small for definite conclusions to be drawn.

Small molecule inhibitors. Small-molecule tyrosine kinase inhibitors inhibit both VEGF receptor and other receptors in the split kinase domain superfamily of tyrosine kinase receptors such as PDGF receptor which is expressed in pericytes. Therefore, an alternative approach to VEGF inhibition involves small-molecule tyrosine kinase inhibitors (Table 6).

Inhibition of the signal transduction pathway of phosphatidylinositol 3-kinase-*AKT*-mammalian target of rapamycin (PI3K-AKT-mTOR) slows down tumor growth and adaptation to hypoxia. Rapamycin and rapamycin analogs such as CCI-779 inhibit *mTOR* activation that causes tumor growth arrest and inhibition of HIF-1α synthesis.[77] Antitumor activity has been demonstrated by CCI-779 administration in patients with an advanced RCC in a phase 2 trial which was well tolerated.[78] Phosphatase and tensin homolog (*PTEN*) gene mutations have been detected to make tumors dramatically more responsive to treatment with CCI-779 than tumors with a normal *PTEN*.[79]

The Ras/Raf signaling pathway is important in tumor cell proliferation and angiogenesis. Activated Ras leads to cell proliferation via the Raf/MEK/ERK pathway by binding to and activating Raf kinase. BAY 43-9006 is an orally bioavailable Raf kinase inhibitor that inhibits tumor cell proliferation by both inhibiting c-Raf and b-Raf. It also inhibits angiogenesis by acting on VEGF receptor 2 and PDGF receptor-β. After a 12-week induction phase with BAY 43-9006, 89 of 106 patients with RCC had a response and 37 experienced tumor shrinkage of more than 25% and 13 had their tumors shrunk by at least 50% in a phase 2, randomized, placebo-controlled

trial.[80]

STI-571 (Gleevec) inhibits PDGF receptor and it has a specificity for *c-KIT* pathway. High *c-KIT* expression has been demonstrated in sarcomatoid RCC; therefore, STI-571 might be useful in the treatment of these tumors.[81]

SU-011248 is an orally bioavailable indolinone that works as a signal transduction inhibitor of the VEGF receptor, PDGF receptor, and c-kit tyrosine kinase. Motzer and colleagues administered SU-011248 orally in a phase 2 study to 63 patients with a metastatic RCC who had failed standard therapy.[82] A partial response was achieved in 33% of patients; while, 37% had a stable disease for less than 3 months. At 6 months, 22% had a partial response. Toxicities were most commonly grade 1 or grade 2 including fatigue/asthenia, nausea, diarrhea, and stomatitis. Grade 3/4 toxicities included lymphopenia, and elevated serum levels of lipase, amylase, and phosphorus.

PTK787/ZK222584 (PTK787) is an oral, selective inhibitor of VEGF receptor-1, VEGF receptor-2, and PDGF receptor-β tyrosine kinases.[53] In a phase 1/2 trial, PTK787 was administered to 45 patients with a metastatic RCC. Among 41 patients evaluated, 2 (5%) partially responded. Minor responses (25% to 50% tumor shrinkage) were detected in 6 patients (15%) and therapy was well tolerated.[83]

Another potential anticancer strategy is the use of drugs that work on the ubiquitin/proteasome system. Bortezomib (PS-341) is a small molecular weight reversible inhibitor of the intracellular 26S proteasome, a large protein (enzyme) complex that may target HIF-1. It may respond to proteasome inhibition and is recently approved by FDA for multiple myeloma and RCC.[6] Drucker and coworkers administered bortezomib (PS-341) to patients with a metastatic disease and of the 32 patients evaluated, 3 achieved a partial response (9%) and the remaining had either stable or progressive disease. All responders had progressed with cytokine therapy. Most of the adverse events were grade 2/3.[84]

HIF-1α is associated with the molecular chaperone, Hsp90. Geldanamycin is an Hsp90 antagonist and promotes degradation of HIF-1α in both normoxia and hypoxia.[85] Therefore, direct inhibition of the HIF activity causes targeting the VHL pathway.

YC-1 is an antiangiogenic anticancer agent which blocks HIF-1α expression at the posttranscriptional level.[86] YC-1 has been demonstrated to decrease the growth of Caki-1 renal carcinoma xenografts in immunodeficient mice.[86]

Histone deacetylase (HDAC) inhibitors are agents which reverse the repression of genes responsible for the regulation of cell cycle and apoptosis. Depsipeptide (FR901228) is a HDAC inhibitor with cytotoxic activity and a response has been demonstrated in a small phase 1 trial in patients with RCC.[87]

GTI-2040 is an antisense compound that targets the ribonucleotide reductase (RNR) R2 subunit, which is an essential enzyme for DNA synthesis and repair. GTI-2040 is being studied in combination with capecitabine and has shown potential against RCC.[88]

BAY 59-8862 is a second-generation taxane and exhibits antiangiogenic activity by downregulating both VEGF and bFGF. In a phase 2 study, 42 patients were evaluated who were administered BAY 59-8862 and there were no complete or partial responders. Stable disease was detected in 6 patients with a median duration of 4.5 months.[89]

Epothilone EP0906 is a microtubular stabilizer that inhibits cell growth. In a phase 2 study, Epothilone EP0906 was administered to 52 patients with advanced RCC. Partial response was detected in 2 patients (at 3 months and 5 months) and 24 patients had a stable disease at 16 weeks of therapy.[90]

Summary and Future Perspectives

The incidence of kidney cancer is increased all around the world. Renal cell carcinoma is the most lethal of the common urological malignancies with 40% eventually dying of cancer progression and the chance of cure in advanced and metastatic cancer is low. Due to the widespread use of imaging modalities, many tumors are diagnosed incidentally with an earlier stage which can be cured by surgery.[91] Currently, surgery is considered as the only curative treatment for localized RCC in which RN and NSS cure most of the patients with an early-stage disease. Laparoscopy is increasingly being performed in the surgical management of kidney tumors particularly for early-stage disease unsuitable for NSS. Laparoscopic RN seems to provide long-term cancer control comparing to open RN.

The typical RCC is a highly vascular tumor with

an extremely poor prognosis in the presence of metastases.[92] The current therapy for metastatic RCC is inadequate and surgery is an important component of the treatment with combined immunotherapy. There has been a tremendous development in oncological urology in the last couple of years, particularly in the treatment of advanced and metastatic cancer. Although chemotherapy was the standard treatment for all advanced urological malignancies, better understanding of the molecular pathways of carcinogenesis individualized targeted and biological treatments.[91] The field of RCC is rapidly undergoing a revolution led by molecular markers and therapies based on molecular targeting. The use of genetic and molecular markers might predict an individual tumor's behavior which could lead to shifting from nonspecific treatments to designing and targeting therapies in selected populations of patients. The hypoxia-inducible pathway plays an important role in epithelial proliferation, cell migration, apoptosis, glucose transport, glycolysis, pH control, and angiogenesis; therefore, it seems to be responsible for the adaptation of RCC to a hypoxic environment, thus, their resistance to radiation and chemotherapy. Inactivation of the *VHL* gene leads to accumulation of HIF factor which causes activation of the following genes: *VEGF*, *PDGF*, *EPO*, *CA9* and *TGFA*.[92] Drugs currently under development target VEGF, VEGF receptor, PDGF receptor and tyrosine kinase receptors, which are necessary for intracellular signal transduction.[92] Promising targeted therapeutic alternatives such as antibodies, tumor vaccines, anti-angiogenesis agents, and small molecule inhibitors seems to have a far less toxicity than traditional therapies on a molecular level although responses are still modest. Current research is being focused on identification of novel agents and treatment modalities with a better antitumor activity.

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