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From the Desk of Director Research

Kidney cancer, also called renal cancer, is a disease in which kidney cells become malignant and grow out of control, forming a tumor. Renal cell carcinoma (RCC) accounts for around 90 percent of all kidney cancers and is highly aggressive and most lethal among urologic malignancies. Each year approximately 273,000 new cases of kidney cancer are diagnosed worldwide, representing about 2 percent of all cancers. Although the number of such cases in Asia is the lowest, the ratio of incidence to mortality is higher. The highest incidences of RCC tend to occur in Western countries. Smoking, overweight, hypertension, and germline mutations in specific genes are the established risk factors for this malignancy. RCC can be either familial or sporadic. Both forms are often associated with distinct genetic mutations, of which the most prominent are the von Hippel-Lindau gene mutations.

Unfortunately, early kidney cancers do not usually cause any signs or symptoms, but larger ones might. Unlike most other cancers, kidney cancer can often be diagnosed fairly without a biopsy. Usually imaging tests give a reasonable amount of certainty that a kidney mass is cancerous or not. Many prognostic factors, such as the TNM staging system, tumor grade, sarcomatoid features, tumor size, performance status, etc, have been identified in RCC.

The radical nephrectomy is considered as the gold standard treatment for localized RCC with contralateral normal kidney. Approximately one-third of the patients present with metastatic disease and up to 40% of the patients suffer recurrence after surgery for clinically localized disease. In metastatic disease, the cure rate is low as it is highly radio- and chemo-resistant. RCC evokes an immune response, which has occasionally resulted in spontaneous and dramatic remissions. However, no satisfactory results exist for patients with advanced RCC at present and the response rate with immunotherapy using INFá and IL-2 is less than 20%.

More recently, there has been the advent of targeted cancer therapies. 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. Selective advances in diagnosis, staging and treatment of patient with RCC have resulted in improved survival of a selected group of patients and overall change in natural history of the disease.

This issue of Cancer News profiles the complexities and advancements in the field of renal cancer, and includes regular articles, such as “Special Feature”, “Guest Article”, “Perspective”, “Watch-Out”, “Research & Development”, “New Technologies”, “Clinical Trials”, “Watch-Out”, “Globe Scan”, and “Cancer Control”.

We appreciate the contribution made by Dr Kumar Prabhash, Professor, Dept of Medical Oncology, Tata Memorial Hospital, Mumbai, for providing the “Guest Article”on “Redefining Treatment Selection to Optimize Patient Outcomes in Renal Carcinoma”.

Suggesations / Comments from the readers are welcome.

Dr D C Doval

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SPECIAL FEATURE

RENAL CELL CARCINOMA – AN OVERVIEW

Introduction

The treatment of renal cell carcinoma (RCC) has undergone many changes during the last several decades. Major advances include increased detection of incidental tumors and a trend towards nephron-sparing surgery and, more recently, a variety of minimally invasive approaches. Even today, RCC remains primarily a surgical disease. It is still considered the paradigm of the chemorefractory tumor, and although immune-based therapies have shown promise, overall response rates remain low. Recent efforts have focused on multimodal strategies in addition to a variety of novel therapeutic approaches.

Incidence

RCC, which accounts for 2% to 3% of all adult malignant neoplasms, is the most lethal of the urologic cancers. Overall, 8.9 new cases are diagnosed per 100,000 population per year in the United States with a male-to-female predominance of 3:2. This is primarily a disease of the elderly, with typical presentation in the sixth and seventh decades of life. The incidence of RCC has increased since 1970s, largely because of more prevalent use of ultrasonography and CT scan. This trend is correlated with an increased proportion of incidentally discovered and localized tumors and with improved 5-year survival rates for patients with this stage of disease. The incidence of advanced tumors per unit population has also increased suggesting that a deleterious change in tumor biology may have occurred.

Etiology

The only generally accepted environmental risk factor for RCC is tobacco exposure. Studies have shown that RCC is more common among individuals with long-standing obesity, low socio-economic status, and urban background, although the causative factors have not been defined. Other potential iatrogenic causes include thorotrast, radiation therapy, and antihypertensive medication; but the relative risks are low.

Pathology

Most RCCs are round to ovoid and circumscribed by a pseudocapsule of compressed parenchyma and fibrous tissue rather than a true histologic capsule. They are not grossly infiltrative, with the notable exception of collecting duct RCC and some sarcomatoid variants. Nuclear features can be highly variable, and a number of grading systems have been based on features like nuclear size and shape and the presence or absence of prominent nucleoli. Fuhrman's system has been most generally adopted and is now recognized as an important independent prognostic factor for RCC. Frank invasion and perforation of the collecting system or renal capsule are found in approximately 20% of cases, although displacement of these structures is a more common finding. One unique feature of RCC is its predilection for involvement of the venous system, which is found in 10% of RCCs. This is most commonly manifested in the form of a contiguous tumor thrombus that can extend into the inferior vena cava as high as the right atrium. Bilateral involvement can be synchronous or asynchronous and is found in 2% to 4% of sporadic RCCs, although it is considerably more common in patients with von Hippel–Lindau disease or other familial forms of RCC. Satellite lesions are often small and difficult to identify by preoperative imaging, intraoperative ultrasonography, or visual inspection; they appear to be the main factor contributing to local recurrence after partial nephrectomy.

Approximately 90 % of renal tumors are RCC. All RCCs are by defenition adenocarcinomas, derived from renal tubular epithelial cells. Clear cell and papillary variants of most RCCs are derived from proximal tubular cells wheras most other histologic subtypes appear to be derived from the more distal elements of the nephron.

Conventional RCC accounts for approximately 70% to 80% of all RCCs, representing the garden variety of RCC. Chromosome 3 alterations and *VHL* mutations are common in conventional RCC. Chromophilic RCC or papillary RCC represents 10% to 15% of all RCCs, although it is more commonly found in certain populations, such as patients with end-stage renal failure and acquired renal cystic disease. Chromophobe cell carcinoma, is a distinctive histologic subtype of RCC that appears to be derived from the cortical portion of the collecting duct . It represents 3% to 5% of all RCCs.

Collecting duct, or Bellini's duct carcinoma is a relatively rare subtype of RCC, accounting for less than 1% of all RCCs .Many reported cases have occurred in younger patients, and are derived from the medulla. Renal medullary carcinoma occurs almost exclusively in association with the sickle cell trait. It is typically diagnosed in young African Americans, often in the third decade of life. It is thought to arise from the calyceal epithelium near the renal papillae but is often highly infiltrative. Sarcomatoid variants of almost all the histologic subtypes of RCC have been described, found in 1% to 5% of RCCs, most

commonly in association with conventional or chromophobic RCC . It is characterized by spindle cell histology, positive staining for vimentin, infiltrative growth pattern, aggressive local and metastatic behavior, and poor prognosis. Unclassified RCC represents a small minority of cases (<3%) of presumed RCC with features that remain indeterminate even after careful analysis.

Clinical Presentation

Because of the sequestered location of the kidney within the retroperitoneum, many renal masses remain asymptomatic and nonpalpable until they are advanced. With the more pervasive use of noninvasive imaging for the evaluation of a variety of nonspecific symptom complexes, more than 50% of RCCs are now detected incidentally. Symptoms associated with RCC can be due to local tumor growth, hemorrhage, paraneoplastic syndromes, or metastatic disease. The classic triad of flank pain, gross hematuria, and palpable abdominal mass is now rarely found. Indicators of advanced disease include constitutional symptoms, such as weight loss, fever, and night sweats; physical examination findings such as nonreducing varicocele and bilateral lower extremity edema suggest venous involvement. A minority of patients present with symptoms directly related to metastatic disease, such as bone pain or persistent cough. Paraneoplastic syndromes are found in 20% of patients with RCC, the most common being hypercalemia, hypertension, polycythemia, hepatic dysfunction and anemia.

Staging and Diagnosis

Until the 1990's, the most commonly used staging system for RCC was Robson's modification of the system of Flocks and Kadesky. International Union Against Cancer proposed the tumor, nodes and metastases (TNM) system of staging which was revised in 2002 by the American Joint Committee on Cancer, which is now the recommended staging system.

The clinical staging of renal cancer begins with a thorough history, physical examination, and judicious use of laboratory tests. Abnormal liver function test results, elevated serum alkaline phosphatase or sedimentation rate, and significant anemia point to the probability of advanced disease. The radiographic staging of RCC can be accomplished with a high-quality abdominal CT scan in most cases. MRI can be reserved primarily for patients with locally advanced malignant disease, possible venous involvement, renal insufficiency, or allergy to intravenous contrast material. Metastatic evaluation in all cases should include a routine chest radiograph, and liver function tests. A bone scan can be reserved for patients with elevated serum alkaline phosphatase or bone pain and chest CT scan can be reserved for patients with pulmonary symptoms or an abnormal chest radiograph. Positron emission tomography has also been investigated for patients with high risk or metastatic RCC, with most studies showing good specificity but suboptimal sensitivity. At present, its best role is for patients with equivocal findings on conventional imaging. The indications for percutaneous renal biopsy or aspiration in the evaluation of renal masses have traditionally been limited. It is indicated in patients suspected of having metastatic disease, renal abscess, or lymphoma, all of which are primarily managed medically or in patients presenting with disseminated metastases or unresectable primary tumors before starting target therapy or in patients with extensive comorbid disease or other contraindications to surgery.

Table 1: International TNM Staging System for RCC

T	:	Primary tumor
TX	:	Primary tumor cannot be assessed
T0	:	No evidence of primary tumor
T1a	:	Tumor < 4.0 cm and confined to the kidney
T1b	:	Tumor > 4.0 cm and <7.0 cm and confined to the kidney
T2	:	Tumor > 7.0 cm and confined to the kidney
T3a	:	Tumor invades adrenal gland or perinephric fat but not beyond Gerotas fascia
T3b	:	Tumor extends into the renal vein (or its segmental branches) or vena cava below diaphragm
T3c	:	Tumor extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	:	Tumor invades beyound Gerota's fascia
N	:	Regional lymph nodes
NX	:	Regional lymph nodes cannot be assessed
N0	:	No regional lymph nodes metastasis
N1	:	Metastasis in a single regional lymph node
N2	:	Metastases in more than one regional lymph nodes
M	:	Distant metastases
MX	:	Distant metastasis cannot be assessed
M0	:	No distant metastasis

Table 2: Stage Grouping

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1 or T2	N1	M0
	T3	N0 or N1	M0
Stage IV	T4	any N	M0
	any T	N2	M0
		anyN	M1

Prognostic Factors

Important prognostic factors for RCC include specific clinical signs or symptoms, tumor-related factors, and various laboratory findings. Stage has proved to be the single most important prognostic factor for RCC. Studies demonstrate 5-year survival rates of 70% to 90% for organ-confined disease and document a 15% to 20% reduction in survival associated with invasion of the perinephric fat. Further studies document 45% to 69% 5-year survival rates for patients with venous tumor thrombi as long as the tumor is otherwise confined to the kidney, and suggesting that the cephalad extent of tumor thrombus is not of prognostic significance as long as the tumor is otherwise confined. The major drop in prognosis comes in patients whose tumor extends beyond Gerota's fascia to involve contiguous organs, which is rarely associated with 5-year survival, and in patients with lymph node or systemic metastases. Lymph node involvement has long been recognized as a dire prognostic sign because it is associated with 5- and 10-year survival rates of 5% to 30% and 0% to 5%, respectively. Systemic metastases portend a particularly poor prognosis for RCC, with 1-year survival of less than 50%, 5-year survival of 5% to 30%, and 10-year survival of 0% to 5%. Tumor grade and histologic subtype are also indicators of prognosis.

The most widely used prognostic factor model for metastatic disease is from the Memorial Sloan Kettering Cancer Centre (MSKCC), which includes five variables: interval from diagnosis to treatment of less than 1 yr, Karnofsky performace status less than 80 %, serum LDH >1.5 times the upper normal limit (UNL), corrected serum calcium >UNL, and serum hemoglobin < lower normal limit. Patients are divided into low risk, intermediate risk and poor risk according to these variables.

Treatment of Localized RCC

Radical Nephrectomy: Surgery remains the mainstay for curative treatment of this disease. The objective of surgical therapy is to excise all the tumor with an adequate surgical margin. Radical nephrectomy (RN) remains the established form of treatment for patients with localized unilateral RCC and a normal contralateral kidney. Radical nephrectomy includes a perifascial resection of the kidney, peri renal fat, regional lymphnodes, and ipsilateral adrenal gland. Open, laparoscopic or robotic surgical technique may be used to perform RN, with equivalent cancer free survival rates.

The surgical approach for radical nephrectomy is determined by the size and location of the tumor as well as by the body habitus of the patient. The NCCN Kidney Cancer Panel recommends lymph node dissection for patients with papable or CT detected enlarged lymph nodes and to obtain adequate staging information in those with nodes that appear normal. Ipsilateral adrenalectomy should be considered for patients with large upper pole tumors or abnormal appearing adrenal glands on CT scan.

Nephron- Sparing Surgery: Nephron-sparing surgery entails complete local resection of a renal tumor while leaving the largest possible amount of normal functioning parenchyma in the involved kidney. Accepted indications for nephron-sparing surgery include situations in which radical nephrectomy would render the patient anephric or at high risk for ultimate need of dialysis. This encompasses patients with bilateral RCC or RCC involving a solitary functioning kidney or if functioning opposite kidney is affected by a condition that might threaten its future function. Nephron-sparing surgery may be an acceptable therapeutic approach in patients who have a single, small (<4 cm) RCC and a normal contralateral kidney. Open, laparoscopic or robotic partial nephrectomy all offer comparable outcomes in the hands of skilled surgeons.

Three-dimensional volume-rendered CT (or MRI) is now established as a noninvasive imaging modality that can accurately depict the renal parenchymal and vascular anatomy. The technical success rate of nephron-sparing surgery for RCC is excellent.

Thermal Ablative Therapies: Thermal ablative therapies, including renal cryosurgery and radiofrequency ablation, have emerged as alternative nephron-sparing treatments of localized RCC. Both can be administered percutaneously or through laparoscopic exposure and thus they offer the potential for reduced morbidity and more rapid recovery. However, long-term efficacy is not established. The ideal candidates for thermal ablative procedures may be patients with advanced age or significant comorbidities who prefer a proactive approach but are not considered good candidates for conventional surgery, patients with local recurrence after previous nephron-sparing surgery, and patients with hereditary renal cancer who present with multifocal lesions for which multiple partial nephrectomies might be cumbersome if not impossible. Tumor size can also be an important factor in selection of patients because the current technology does not allow reliable treatment of lesions larger than 3.5 cm in diameter. Other exciting new technologies, such as high-intensity focused ultrasound and frameless, image-guided radiosurgical treatments (CyberKnife), are also under development and may allow extracorporeal treatment of small renal tumors in the future.

***Observation*:** Patients with small, solid, enhancing, well-marginated, homogeneous renal lesions, who are elderly or poor surgical risks, can safely be managed with observation and serial renal imaging at 6-month or 1-year intervals.

Treatment of Locally Advanced RCC

Inferior Vena Caval Involvement: Involvement of the IVC with RCC occurs in 4%-10% of patients. Staging of the level of IVC thrombus is as follows: (I), adjacent to the ostium of renal vein; (II), extending up to the lower aspect of the liver; (III), involving the intrahepatic portion of the IVC but below the diaphragm; and (IV), extending above the diaphragm. Surgical removal offers the only realistic hope for cure for most patients. Resection of a caval or atrial thrombus may require the techniques of veno-venous or cardipulmonary bypass, with or without circulatory arrest.

Locally Invasive RCC: Duodenal and pancreatic invasion is uncommon and a poor prognostic sign. Because surgical therapy is the only effective way to manage RCC, extended operations with en bloc resection of adjacent organs are sometimes indicated. Complete excision of the tumor, including resection of the involved bowel, spleen, or abdominal wall muscles, is the aim of therapy. The role of radiation therapy in the treatment of locally extensive RCC is controversial.

Adjuvant Therapy for RCC: The majority of postoperative adjuvant trials in patients with resected renal cancer have been negative, and the standard of care remains observation. Trials using targeted oral agents, such as sorafenib or sunitinib, are underway for the population of patients with surgically resectable RCC, and who are at high risk for recurrence.

Treatment of Metastatic RCC

Nephrectomy: Approximately one-third of patients with RCC have metastatic disease at the time of initial diagnosis (synchronous metastatic disease), and 40% to 50% will develop distant metastases after initial diagnosis. A small subset of patients with potentially surgically resectable primary RCC and a solitary resectable metastatis are condidates for nephrectomy and surgical metastatectomy. Palliative nephrectomy can be done for recurrent hematuria or significant pain or paraneoplastic syndromes. Cytoreductive nephrectomy followed by systemic treatment should be considered in patients with synchronous metastatic disease. Careful selection of patients remains of paramount importance. Individuals with advanced symptoms, metastases in critical areas (central nervous system, spinal cord compression), major organ dysfunction, and significant comorbid illnesses are not candidates for such approaches.

Hormonal Therapy: The use of hormonal therapy for patients with metastatic RCC has minimal value.

Chemotherapy: Currently available data of chemotherapy do not demonstrate reproducible antitumor activity or improvement in survival of patients treated for metastatic clear cell carcinoma. In patients with metastatic non clear cell malignant neoplasms or tumors with sarcomatoid differentiation, various agents including doxorubicin and gemcitabine may have clinical activity.

Radiation Therapy: At present, the main role of radiation therapy for patients with metastatic RCC is for the palliation of symptomatic osseous metastases**.**

Adoptive Immunotherapy and Vaccines: At present, use of adoptive immunotherapy and tumor vaccines remains investigational.

Cytokine Therapy: Until recently, systemic treatment options for metastatic RCC were limited to cytokine therapy. The therapeutic potential of cytokines and immunotherapy has shown real but limited efficacy. Interferon alfa and IL-2 have been tested alone or in combination with overall response rates ranging from 13%-20%.

Targeted Therapy: Targeted therapy utilizing tyrosine kinase inhibitors and mammalian target of rapamycin (mTOR) inhibitors are used widely in first and second-line treatments. To date, seven such agents have been approved by FDA for the treatment of advanced RCC: sunitinib, sorafenib, pazopanib, axitinib, temsirolimus, everolimus and bevacizumab in combination with interferon. With gradually increased usage of these drugs, their role in neoadjuvant and adjuvant setting is also being studied.

Supportive Care

Supportive care remains a mainstay of therapy for all patients with metastatic RCC. A biphosphonate or a RANK ligand inhibitor is indicated for selected patients with bony metastases. Treatment for the palliation of symptoms includes optimal pain management.

Multimodal Therapy

The optimal timing of adjuvant nephrectomy in the setting of multimodality treatment remains unclear. An aggressive surgical approach to RCC often offers the best chance for a long-term cure. Salvage surgery for removal of residual metastatic lesions may extend survival for some patients with metastatic RCC. Selection of patients clearly plays a role.

(Dr Samir Khanna, Consultant; Dr Sudhir Rawal, Sr Consultant and Director Surgical Oncology; Dept of Genito-Uro Oncology)

GUEST ARTICLE

REDEFINING TREATMENT SELECTION TO OPTIMIZE PATIENT OUT COMES IN RENAL CARCINOMA

Introduction

Renal cancer, although relatively rare, accounts for 3-4% of all adult malignancies,[1] with a steady increase in incidence in recent years; globally, in 2008, almost 2.7 lakh new cases of renal cancer were registered, and almost 1.1 lakh renal cancer deaths were recorded. Renal cancer is more frequent in the developed world, with the highest incidence rates in Europe, North America and Australia, and relatively lower incidence rates in India, Japan, Africa and China.[2,3,4] Renal cell carcinoma (RCC) accounts for approximately 85-90% of all kidney tumors, and the most common histological subtype of RCC is clear cell RCC (75-80% of all RCC). Non-clear cell RCC, which accounts for about 20-25% of RCC, includes, among other subtypes, papillary and chromophobe RCC.[3]

Many risk factors, such as obesity, smoking, hypertension, etc., have been implicated in the etiopathogenesis of RCC; however, no causality has been demonstrated yet.[3] RCC is usually asymptomatic, and as many as 50% of the cases are diagnosed incidentally on radiology. It is only in the advanced stages of the disease, when symptoms such as weight loss, hematuria and an abdominal mass, manifest; 20% of patients have regional spread, and 30% have metastatic disease at presentation. Diagnosis is also often obscured by non-specific symptoms such as those pertaining to metastatic disease (bone pain, respiratory symptoms), those arising from other organ involvement and/or paraneoplastic syndromes.[5,6]

Surgery remains the mainstay of the management of RCC; however, the role and appropriate timing of nephrectomy in the current era of targeted therapeutic agents is being evaluated in multiple studies. Despite surgery for localized disease, one-third of patients subsequently relapse and develop metastaticdisease. The prognosis for patients with metastatic disease is poor, with a five-year survival rate of~10%.[7] Metastatic RCC is known to be resistant to hormonal therapy, conventional chemotherapy and radiotherapy. Until recently, cytokine-based immunotherapy with interleukin-2 (IL-2) and interferon-α(IFN-α)comprised the standard of care for metastatic RCC (mRCC). However, these treatments were shown to have limited efficacy in a majority of mRCC cases and were associated with substantial toxicities. The need for better treatment approaches to mRCC and recent developments in our comprehension of the molecular biologic landscape in mRCC has led to the identification of specific etiopathogenetic cascades and targets through ongoing research.

The origin of the molecular etiopathogenetic mechanisms in RCC have been traced to sporadic or genetic aberrations (observed in hereditary and familial renal cancer syndromes, such as the von Hippel Lindau syndrome, Birt Hogg Dube syndrome and hereditary papillary RCC).[3] This understanding has spurred extensive research on molecular targeted therapy in RCC and has revolutionized our treatment approach to RCC. The common underlying etiopathogenetic theme in RCC is unregulated angiogenesis, which arises predominantly from the disturbances in hypoxia signaling,[8] and the critical targets in this cascade include the vascular endothelial growth factor (VEGF) and the mammalian target of rapamycin (mTOR).[9] As a result of identification of these targets, as many as seven new therapies for mRCC have been approved by various drug regulatory agencies in less than a decade: these include VEGF receptor tyrosine kinase inhibitors (VEGFR-TKIs) such as Sorafenib, Sunitinib, Pazopanib and the most recent Axitinib, a monoclonal antibody against VEGF (Bevacizumab), and the mTOR inhibitors, Temsirolimus and Everolimus. This article provides an overview of the available data on the recommended clinical use of these agents with the aim of optimizing therapeutic outcomes in mRCC, and also raises some important unanswered questions with the hope that ongoing research will address them in the future.

Treatment-naive Patients with mRCC

For the treatment of treatment-naive patients with metastatic clear-cell RCC, the National Comprehensive Cancer Network (NCCN) guidelines currently offer category 1 recommendations to 4 agents, namely, Sunitinib, Bevacizumab + IFN-α, Pazopanib and Temsirolimus (in patients with poor prognostic risk). Each of these agents individually has favorable evidence from at least one Phase III study for use in treatment-naive clear-cell mRCC.[10]

In this setting, Sunitinib was the first agent to be approved by the US-FDA in 2006, based on the results from a Phase III trial (N = 750) reported by Motzer, et al.,[11] which compared Sunitinib versus IFN-α in treatment-naive patients with mRCC. Patients received

oral Sunitinib 50 mg once daily for 4 weeks in 6-weekcycles (n = 375) or subcutaneous IFN-α, 9 million units (MU) three times weekly (n = 375). Sunitinib treatment resulted in a statistically significant, favorable progression-free survival (PFS) of 11 months versus IFN-α (5 months; Hazard Radiot (HR): 0.54); however, it failed to provide a significantly superior overall survival (OS) benefit (Sunitinib versus IFN-α: 26.4 versus 21.8 months; HR: 0.82).Most common adverse events associated with Sunitinib compared with IFN-á were diarrhea (61% versus 15%), fatigue (54% versus 52%), and nausea (52% versus 35%), and the most common grade 3/4 treatment-related adverse events with Sunitinib were hypertension (12%), fatigue (11%), diarrhea (9%), and hand-foot syndrome (9%).[11]

The approval of Bevacizumab + IFN-α for treatment-naive advanced RCC succeeded the AVOREN trial[12] where the efficacy of the combination was assessed in 649 patients. Patients received IFN-α 9 MU 3 times weekly + Bevacizumab 10 mg/kg IV every 2 weeks (n = 327) or IFN-α 9 MU 3 times weekly (n = 322). The median PFS was significantly longer in the Bevacizumab + IFN-α group than it was in the IFN-α plus placebo group (10.2 versus 5.4 months), while the OS was similar across both the groups (23.3 versus 21.3 months). Similarly, in a Phase III trial (CALGB)[13] with 732 patients, OS favored Bevacizumab combined with IFN-α (18.3 months) compared to IFN-α monotherapy (17.4 months), but the difference was not significant. The treatment-related toxicities were higher in the Bevacizumab + IFN-α group; however, hypertension was suggested to be a biomarker of outcome for the Bevacizumab + IFN-α arm.

Pazopanib, a more selective VEGFR-TKI with remarkable VEGFR-2 inhibitory potential, was recently approved in 2009 for treatment-naive advanced RCC. In a pivotal Phase III trial (N= 435)[14] that included treatment-naïve (n = 233) and cytokine-pretreated (n = 202) patients with advanced RCC, the trial subjects were treated with either Pazopanib (800 mg/day orally; n = 290) or placebo (n = 145). The PFS favored Pazopanib among treatment-naive patients with mRCC (11.1 months versus 2.8 months with placebo). Pazopanib demonstrated acceptable safety and tolerability and most adverse events related to Pazopanib treatment were grade 1 or 2 and were clinically manageable. A possible criticism of this pivotal trial is that it was conducted with a placebo group instead of an active comparator from among the therapeutic options already approved for this indication.[7] Therefore, the COMPARZ[15] (evaluating the efficacy of Pazopanib versus Sunitinib) and PISCES[16] (patient and physician preference for Pazopanib versus Sunitinib) were conducted. The COMPARZ trial demonstrated the non-inferiority of Pazopanib as compared to Sunitinib (median PFS: 8.4 months versus 9.5 months; HR: 1.047), a lower incidence of fatigue, hand-foot syndrome, mucositis and hematological toxicities, and better quality of life Quality of Life (QoL) scores. In the uniquely designed PISCES trial, 70% of patients and 61% of physicians preferred Pazopanib over Sunitinib owing to better QoL and less fatigue, thus making Pazopanib a welcome addition to the physicians' armamentarium to treat mRCC.

Temsirolimus, the first mTOR inhibitor to be approved for renal cancer, carries an NCCN category 1 recommendation for the first-line treatment of patients with advanced RCC who have a high prognostic risk based on the presence of 3 or more of the 6 risk stratification criteria (serum lactate dehydrogenase level of more than 1.5 times the upper limit of normal, a corrected serum calcium level more than the upper limit of normal, a hemoglobin level less than the lower limit of normal, a Karnofsky performance score <70, multiple organ metastases and <1 year duration between diagnosis and treatment). The approval of Temsirolimus in this setting was based on evidence from the Phase III global advanced renal cell carcinoma (ARCC)[17] trial (N = 626), the largest ever trial that included as many as 94% advanced RCC patients with a poor prognostic risk. This three-arm trial compared Temsirolimus monotherapy (intravenous; 25 mg/week; n = 209), IFN-α monotherapy (subcutaneous; 3-18MU three times weekly; n = 207) or combination therapy with Temsirolimus (intravenous; 15 mg/week) and IFN-α (subcutaneous; 6MU three times weekly; n = 210). Temsirolimus monotherapy provided a significant OS benefit (10.9 months versus 7.3 months (IFN-α monotherapy) and 8.4 months (combination arm). Temsirolimus monotherapy was also associated with the fewest grade 3/4 adverse events and fewest dose reductions or delays, and the benefit was consistent across various subgroups, particularly those over 65 years of age and those with non-clear cell RCC, and was independent of the nephrectomy status of the patients.

Cytokine Failure in mRCC

Although cytokines comprised the standard of care for mRCC in the pre-targeted therapy era, they had been shown to be associated with significant toxicities, with response rates of 10-20% and a marginal survival benefit.[18] This necessitated the search for better agents that could be applied in case of cytokine failure in mRCC. Currently, NCCN guidelines offer category 1 recommendations to

Sorafenib, Pazopanib and Axitinib in this setting. While both Sorafenib and Pazopanib individually have evidence from placebo-controlled Phase III trials in this setting, Axitinib is the only agent that has shown superiority over Sorafenib in the head-to-head comparative Phase III AXIS trial.

The USFDA approval for Sorafenib in this setting was provided on the basis of evidence from the Phase III TARGET trial (N = 903)[19] that randomized cytokine-pretreated patients with mRCC to receive Sorafenib (400 mg twice daily orally; n = 451) or placebo (n = 452). Sorafenib was associated with a significant PFS (5.5 versus 2.8 months; HR: 0.44; planned interim PFS analysis) and OS advantage (17.8 versus 14.3 months; HR: 0.78; per-protocol analysis after adjusting for cross-over). Adverse events were generally manageable; hypertension and cardiac ischemia were rare serious adverse events that were more common in patients receiving Sorafenib than in those receiving placebo. The pivotal placebo-controlled, Phase III trial of Pazopanib[14] enrolled 202 cytokine-pretreated patients with mRCC; a subgroup analysis for median PFS showed a trend in favor of Pazopanib (7.4 months versus 4.2 months; HR: 0.54) with manageable toxicities, which ultimately led to the USFDA approval of Pazopanib in this setting.

The only agent to be tested in a head-to-head Phase III comparative trial (the AXIS trial) in this setting is Axitinib.[20] This trial randomized 723 patients with advanced RCC who had progressed on first-line therapy to receive Axitinib (5 mg twice daily, oral; n = 361) or Sorafenib (400 mg twice daily, oral; n = 362). In a planned subset analysis of the cytokine-pretreated patients in this trial (n = 253), Axitinib was shown to be superior to Sorafenib (median PFS, 12.1 months versus 6.5 months; HR: 0.46), with a manageable toxicity profile, which led to its USFDA approval in this setting.

VEGFR-TKI Failure in mRCC

Although VEGFR-TKI-based therapies provide significant improvements over cytokine immunotherapy in mRCC, VEGFR-TKI resistance develops within 6-11 months in most patients.[21] Thus, for patients with mRCC there is a compelling need for effective treatment following progression on a VEGFR-TKI. As resistance develops, subsequent disease progression can be rapid, particularly if treatment is stopped. Initial evidence suggests that reemergence of tumor-associated vasculature (i.e., angiogenic escape) is common with continued VEGF suppression and is believed to occur by either intrinsic or adaptive mechanisms, which involve the up-regulation of alternative angiogenic signals beyond VEGF. For patients who have an objective response or stable disease (SD) on VEGFR-TKI treatment and then experience progressive disease, one possible approach to overcoming resistance is sequential treatment with a different VEGFR-TKI. Although a few small retrospective datasets indicate that treatment with a second VEGFR-TKI is often effective after failure of a first VEGFR-TKI, this conclusion has been called into question by the results of prospective studies. Moreover, sequential therapy with VEGFR-TKIs have often shown to result in cumulative toxicities and increased incidence of dose reductions and / or treatment discontinuation.

An alternative approach to VEGFR-TKI failure in mRCC is the application of agents that target a different pathway, i.e., mTOR inhibition. This formed the rationale for the RECORD-1 trial,[22] the first, largest, placebo-controlled Phase III trial of Everolimus in VEGFR-TKI failure. This trial randomized 416 patients with mRCC that had failed previous therapy with Sunitinib (n = 184) or Sorafenib (n = 124) or both (n = 108) to receive either Everolimus (10 mg/ day orally; n = 277) or placebo (n = 139). Notably, prior treatment with IFN-α, IL-2, Bevacizumab, and chemotherapy was permitted, and on the experimental arm, a total of 179 patients (65%) were enrolled that had also received prior immunotherapy.[23] Everolimus was associated with a significantly better PFS (4.9 months versus 1.9 months; HR: 0.33), and the PFS benefit was consistent across subgroups. Notably, the beneficial effect of everolimus (HR: 0.33) is the strongest among all other molecules (HR ranging from 0.44 to 0.73) tested in phase III trials, in terms of PFS, with a 67% reduction in the risk of disease progression. Moreover, an impressive PFS benefit with Everolimus was recorded despite it being tested in the cohort of patients with the most aggressive natural history of the disease ever examined in a Phase III mRCC design.[24] Everolimus was well tolerated and its therapeutic benefits were associated with sustained health-related QoL. Clinical practice guidelines in the US and Europe therefore, uniformly recommend Everolimus as the standard of care in mRCC that has failed first-line VEGFR-TKI therapy, based on the robust clinical evidence from this study.

The post-VEGF-TKI space had been absent, a challenge until the results of the AXIS trial, led to the approval of Axitinib in this setting.[23] Of the 723 patients enrolled on this trial, 390 had received prior therapy with Sunitinib, and in these patients, Axitinib yielded a modest benefit in PFS as compared with Sorafenib (4.8 versus 3.4 months).[20]

Discussion & Conclusions

The erstwhile relative dearth of treatment options for mRCC has been transformed into an embarrassment of the riches, owing to our much improved understanding of the various etiopathogenetic signal transduction pathways and targets in mRCC. As many as 7 new agents for mRCC have been approved in less than a decade. However, therapy with these targeted agents is rarely curative, and therapeutic resistance is common; therefore, patients often have to rely on multiple lines of therapy for a sustained clinical benefit.[23]

In the first-line (treatment-naive) setting, Pazopanib appears to represent a contemporary thinking with a better tolerability profile and non-inferior efficacy as compared the classical proven option of Sunitinib. In the cytokine-pretreated setting, Axitinib appears to be the most effective agent, with a median PFS of 12.1 months. In the VEGFR-TKI setting, the PFS estimates from AXIS and RECORD-1 appear to be somewhat comparable. However, it is critical to bear in mind that 53% of patients enrolled in RECORD-1 had received prior immunotherapy in addition to prior VEGFR-TKI; these results give a pause in interpreting the slight numerical advantage in PFSobserved with Axitinib therapy in this subgroup.[23]AXIS thus provides compelling rationale for the use of Axitinib in the setting of cytokine-refractorydisease. In the context of disease refractory to VEGF-directedtherapy, however, it is not clear that Axitinib yields meaningful benefit beyond existing second-line options, such as Everolimus, which remains the recommended standard of care in the VEGFR-TKI failure setting. Head-to-head comparative trials between these agents are warranted to enable a clear mandate on the superiority of one agent over the other in each of these settings.

In case of mRCC progression beyond second-line therapy, currently, there exists no level 1 evidence for any targeted agent, although Dovitinib[25] is being studied in a Phase III trial in this setting. However, in clinical practice, reintroduction of a VEGFR-TKI following disease progression on a VEGFR-TKI and an mTOR inhibitor is increasingly being applied, based on the sparse data available.[21]

The advent of many targeted agents and ongoing research on many more is anticipated to significantly improve the prognosis of mRCC. However, there remain many unanswered questions, including the role of adjuvant therapy, the optimal timing of nephrectomy, sequential versus combination therapy, the exact sequence of targeted agents, right therapy for patients with specific comorbid conditions, etc. In the future, the clinician's priority would be the optimal identification and application of targeted agents to balance the clinical tumor response with the QoL of the patient. Ongoing studies on targeted agents in mRCC will provide insights into the most optimal management approaches for mRCC and further enhance survival in these patients.

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PERSPECTIVE

MOLECULAR BIOLOGY OF RENAL CANCERS

Renal cell carcinoma (RCC) represents approximately 85% of the neoplasms that arise in adult kidneys. Although RCC mostly occurs in a sporadic form, several inherited RCC syndromes and familial RCC cases have been reported. Around 4% are associated with hereditary cancer syndromes (1). Despite their rarity, these have provided important insights into the molecular pathogenesis of this tumor. The cloning of susceptibility genes that are involved in familial predisposition has offered entry points into the signaling pathways that are deregulated in sporadic RCC. Sporadic RCC also harbor similar molecular aberrations as familial RCC with a difference that they are in somatic cells and later are in germ cells, which are passed to the families. The table below gives a broad overview of the tumor types with their genetic and syndromic relationships.

Non-Familial (Sporadic) RCC

***Conventional RCC: Chromosome 3 Connection*:** Many chromosome 3 translocations have been reported in familial as well as sporadic cases. Through loss of heterozygosity (LOH) studies in sporadic RCCs, three main common regions of allelic loss could be defined: 3p12-14, 3p21-22, and 3p25-26. Chromosome transfer studies revealed that 3p12–14 sequences could suppress tumorigenic properties of RCC-derived cell lines, thus implying the presence in this region of a gene(s) involved in tumor development. Similar results were obtained for the 3p21 region. The third tumor suppressor region on 3p is 3p25–26. The most relevant RCC-related gene within this region is the Von Hippel Lindau (VHL) gene.

VHL: A Classical Tumor Suppressor Gene: As proposed by Knudson's two-hit model, inactivation of the VHL gene was observed in 100% of the tumors analyzed in VHL families and in a significant proportion of sporadic conventional RCCs (2). Moreover, transfection studies with the wild-type VHL gene revealed suppression of growth in both VHL-deficient RCC cell lines and in VHL-null RCC cells, thus supporting the tumor suppressor function of this gene. Several signaling pathways appear to be involved, one of which points to a role of pVHL in protein degradation and angiogenesis. The alpha domain of pVHL forms a complex with elongin B, elongin C, Cul-2 and Rbx1, which has ubiquitin ligase activity, thereby targeting cellular proteins for ubiquitinization and proteasome mediated degradation. The domain of the VHL gene involved in the binding to elongin is frequently mutated in VHL-associated neoplasms. The beta-domain of pVHL interacts with the alpha subunits of hypoxia-inducible factor 1 (HIF-1) which mediates cellular responses to hypoxia. Under normoxic conditions, the beta subunit of HIF is hydroxylated on to one of two proline residues. Binding of the hydroxylated subunit pVHL causes polyubiquitination and thereby targets HIF-alpha for proteasome degradation. Under hypoxic conditions or in the absence of functional VHL, HIF-alpha accumulates and activates the transcription of hypoxia inducible genes, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF-β), transforming growth factor (TGF-α) and erythropoietin (EPO). VEGF has been targeted as a novel therapeutic approach using neutralizing anti-VEGF antibody. There are studies that suggest that pVHL is involved in the control of cell cycle exit, i.e. the transition

Table: Tumor Types with Their Genetic and Syndromic Relationships

Tumor type	Locus	Gene	Pathway	Syndrome
Clear cell	3p25 3p14 3p21 17p11	VHL FHIT RASSF1A BHD	VEGF TGF - β AMPK - mTOR	vonHippel-Lindau Familial clear cell RCC Birt - Hogg-Dube
Papillary type 1 type 2	7q31.1 9q34 16p13 1q25	MET FH FRA7G TSC1 TSC2 HRPT2	MET - HGF VEGF TGF-β mTOR mTOR	Hereditary papillary RCC, Hereditary leiomatosis Tuberous sclerosis complex Hyperparathyroidism - jaw tumor
Chromophobe	17p11	BHD	AMPK - mTOR	Birt-Hogg-Dube
Oncocytoma	17p11 9q34 16p13	BHD TSC1 TSC2	A M P K - m T O R mTORmTOR	Birt-Hogg-Dube Tuberous complex Tuberous
Collecting duct carcinoma	-1q32, -6, -8p, -9p, -13q,- 19q32, -21q	UNKOWN	Unknown	none
Renal carcinoma associated with Xp11.2 translocation	-8p, -9p, -11q, +12q, +16q+17, +20q	PSF-TFE3 PRCC-TFE3 CTLC - TFE3 ASPL-TFE3 Non0 - TFE3	None	none
Mucinous tubular and spindle cell carcinoma	-8p, -9p, -11q, +12q, +16q+17, +20q	Unknown	Unknown	Unknown

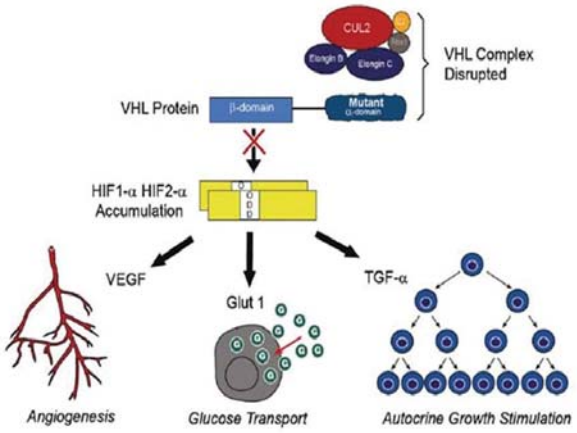

Figure A. VHL gene mutation allows accumulation of HIF, which causes activation of downstream pathways for angiogenesis, glucose transport, and growth.

from the G_2 into quiescent G_0 phase, possibly by preventing accumulation of the cyclin-dependent kinase inhibitor p27(4). Another study showed that only wild-type but not tumor derived pVHL binds to fibronectin(5). As a consequence, VHL-/- RCC cells showed a defective assembly of an extracellular fibronectin matrix. Through a down-regulation of the response of cells to hepatocyte growth factor/ scatter factor and reduced levels of tissue inhibitor of metalloproteinase 2 (TIMP-2), pVHL deficient tumor cells exhibit a significantly higher capacity for invasion.

Other Candidate Genes on 3p: Many associations of RCC have been seen with 3p.The tumor suppressor gene on 3p12–14 ,RASSF1A showing silencing by hypermethylation, transforming growth factor –b type II receptor ,TGE-a, DRR1,OGG1 are shown to be down regulated in RCC(6).

Papillary RCC: An Impaired Mitotic Checkpoint: In papillary RCCs, a combination of gain of chromosomes 7 and 17 and loss of the Y chromosome have been found. In addition, t(X;1)(p11;q21) and variants thereof have repeatedly been encountered in a subgroup of these tumors. Positional cloning of the translocation breakpoint revealed an in-frame fusion of the TFE3 gene on the X chromosome to a novel gene, PRCC, on chromosome 1. The in-frame fusion results in two fusion genes, TFE3PRCC and PRCCTFE3, which are both expressed in t(X;1)-positive tumor cells. These lead to mitotic checkpoint defect through interference with MAD2B binding. (1)

Familial RCC

Clear Cell Carcinoma (VHL Gene): The von Hippel-Lindau (VHL) disease is inherited through an autosomal dominant trait and is characterized by the development of capillary haemangioblastomas of the central nervous system and retina, clear cell renal carcinoma, phaeochromocytoma, pancreatic and inner ear tumors. The syndrome is caused by germline mutations of the VHL tumor suppressor gene, located on chromosome 3p25-26. The gene has already been decribed.

Hereditary Papillary Renal Carcinoma (HPRC)

Definition: Hereditary papillary renal carcinoma (HPRC) is an inherited tumor syndrome characterized with an autosomal dominant trait, and by late onset, multiple, bilateral papillary renal cell tumors of type 1 and no documented extrarenal manifestations.MET oncogene is responsible for the disease, which maps to chromosome 7q31. MET codes for a receptor tyrosine kinase. Furthermore, nutrient-stimulated HGF-MET signaling induces phosphorylation of serine–threonine protein kinase 11 (STK11or LKB1) through the RAS–ERK pathway, implicating MET in the LKB1-AMPK–mTOR nutrient and energy sensing pathway. Of particular interest for renal carcinogenesis is the observation that MET and VHL signaling pathways intersect via pVHL-mediated regulation of HIF function. HIF stabilization through hypoxia or loss of VHL function results in transcriptional upregulation, and therefore promotion of the transforming potential of the c-MET receptor . This crosstalk between VHL and c-MET pathways may explain why clear-cell and papillary histologies often coexist in the same tumor (7).

Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)

Definition: Hereditary leiomyomatosis and renal cell cancer is an autosomal dominant tumor syndrome caused by germline mutations in the FH gene. It is characterized by predisposition to benign leiomyomas of the skin and the uterus. Predisposition to renal cell carcinoma and uterine leiomyosarcoma is present in a subset of families.

Genetics: HLRCC harbours FH mutation, which causes FH deficiency. It is a recessive disease caused by biallelic germline.FH is located in chromosome 1q42.3-q43, consists of 10 exons, and encodes a 511 amino acid peptide. Mitochondrial FH acts in the tricarboxylic acid (Krebs) cycle catalyzing conversion of fumarate to malate. In patients with FH deficient cells, it has been proposed that the inactivation of this enzyme might lead to a hypoxic environment that can favour renal carcinogenesis. FH inactivating mutations increase fumarate levels, and

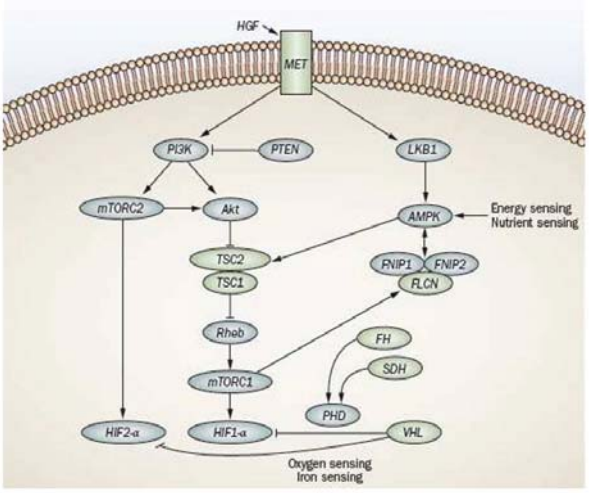

Figure B. HGF-MET pathway. Crosslinks between other energy, iron and oxygen-sensing pathways.

consequently the concentration of the fumarate precursor succinate. The high levels of succinate in the cytoplasm lead to stabilization of HIF-1% subunits and transcriptional upregulation of hypoxia-inducible genes, such as VEGF and GLUT1. Thus, these factors are critically important to increase vasculature and glucose transport in RCC cells, thereby contributing to the highly aggressive nature of HLRCC-associated renal tumors.

Birt-Hogg-Dubé Syndrome (BHD)

Definition: Birt-Hogg-Dubé (BHD) syndrome is a syndrome characterized by benign skin tumors, specifically fibrofolliculomas, trichodiscomas and acrochordons over neck and face in the third or fourth decade of life. Multiple renal tumors resembling mainly chromophobe and clear cell renal carcinoma and renal oncocytoms are seen. Spontaneous pneumothoraces are also frequent in patients with BHD syndrome. The age at clinical manifestation is approximately 50 years and the mean number of tumors present is 5 per patient. Metastatic disease is rare and appears to occur only if the primary tumor has a diameter of >3 cm.

Genetics: BHD syndrome is a rare autosomal dominant condition with incomplete penetrance. The BHD gene maps to chromosome 17p11.2. It codes for a novel protein called folliculin whose function is unknown currently. Affected family members typically show frameshift mutations, ie insertions, stop codons, deletions. A mutational hot spot present in more than 40% of families was identified in a tract of 8 cytosines. LOH analyses and assessment of promoter methylation indicate that BHD is also involved in the development of a broad spectrum of sporadic renal cancers(7).

Familial Chromosome 3: The translocations are different but in all families the breakpoints map to the proximal p-and q-arms of chromosome 3. Affected family members carry a balanced chromosomal translocation involving chromosome 3. The mode of inheritance is autosomal dominant. Translocations vary among different families and this may affect penetrance. Loss of the derivative chromosome 3 through genetic instability is considered the first step in tumor development, resulting in a single copy of VHL. The remaining VHL copy may then be mutated or otherwise inactivated. However, this mechanism involving VHL is hypothetical, as affected family members do not develop extrarenal neoplasms or other VHL manifestations.

Summary

Molecular genetic analysis of familial and non-familial cases of conventional renal cell carcinoma (RCC) revealed a critical role(s) for multiple genes on human chromosome 3. For some of these genes, e.g. VHL, such a role has been firmly established, whereas for others, definite confirmation is still pending. Additionally, a novel role for constitutional chromosome 3 translocations as risk factors for conventional RCC development is rapidly emerging. Also, several candidate loci have been mapped to other chromosomes in both familial and non-familial RCCs of distinct histologic subtypes. The MET gene on chromosome 7, for example, was found to be involved in both forms of papillary RCC. A PRCC–TFE3 fusion gene is typically encountered in t(X;1)-positive non-familial papillary RCCs and results in abrogation of the cell cycle mitotic spindle checkpoint in a dominant-negative fashion, thus leading to RCC.

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NEW TECHNOLOGIES

Alternative to Biopsy

Combining positron emission tomography/computed tomography (PET/CT) scanning with iodine-124 (^{124}I)-girentuximab offers an effective noninvasive method to diagnose clear cell renal cell carcinoma (ccRCC) in patients who present with a renal mass, suggested by a study at Columbia University, USA. This was an open-label multicenter study of ^{124}I–girentuximab plus PET/CT involving 195 patients who were planned for resection. ^{124}I–girentuximab was well tolerated by all the patients. ^{124}I–girentuximab-PET/CT identified the presence of ccRCC with a mean sensitivity of 86.2% (95% CI, 75.3% to 97.1%) while the use of radioactive antibody in combination with CECT showed a significantly lower mean diagnostic sensitivity of 75.5% (95% CI, 62.6% to 88.4%). The study represents the first clinical validation of a molecular imaging marker for malignancy. The new method can accurately and noninvasively identify ccRCC, with potential utility for designing the best management approaches for patients with renal masses.

(J Clin Oncol, Jan 10, 2013)

Biomarkers for Early Detection of Kidney Cancer

A new immunoassay that tests for the presence of nicotinamide N-methyltransferase (NNMT), L-plastin (LCP1), and nonmetastatic cells 1 protein (NM23A) may be an effective method for early detection of malignant kidney cancer, according to a study conducted at Yonsei University Health System in Seoul, Korea. A total of 189 participants were divided into two cohorts; control group including healthy and benign tumors (n = 102) and the test group of patients with kidney cancer (n = 87). The concentrations of NNMT, LCP1 and NM23A in plasma samples in all participants were measured and found to be highly elevated in patients with kidney cancer in contrast to individuals in the control group. For example, the median level of NNMT concentration in healthy controls was 68 pg/mL compared with 420 pg/mL cancer in patients. The results indicated that the immunoassay was highly accurate as it correctly identified 94.4% of the samples from kidney cancer patients. The composite assay is a promising novel serum marker assay for the early detection of malignant kidney tumors covering subtypes of RCC with high diagnostic characteristics.

(ScienceDaily, Mar 11, 2013)

New Prognostic Marker

Researchers at the University of Toronto, Canada, have found the chromatin modelling gene ARID1A (AT-rich interactive domain-containing protein 1A) as a new prognostic marker in clear cell renal cell carcinoma (ccRCC). ARID1A is a member of SW1/SNF (switch/sucrose nonfermentable) family and has been found to be down-regulated frequently in ccRCC. The immunohistochemistry (IHC) results showed that 67% of ccRCC had significantly lower expression of BAP250a, the corresponding protein of gene ARID1A. Simultaneously, in silico mRNA expression analysis on 404 ccRCC tumors and 167 normal kidney cortex samples using publicly available databases was performed and it confirmed the significant down-regulation of ARID1A in 68.8% of patients. The decreased BAF250a protein, ARID1A and mRNA expression were also correlated with tumor stage and grade. BAF250 retained its prognostic significance even after controlling for other confounders in the multivariate analysis. BAF250a IHC is easy to perform and could be incorporated in laboratory practice to enhance the accuracy of existing prognostic models. The study results indicate that both protein and mRNA levels of ARID1A are statistically significant prognostic markers for ccRCC.

(Am J Pathol, Apr 2013)

Sunitinib Beneficial for Renal Cell Carcinoma Patients

The findings of a study show that patients with metastatic renal cell carcinoma did not have accelerated tumor growth after treatment with sunitinib in comparison to some study results in animals. The data from the pivotal phase III trial comparing sunitinib with interferon alfa in patients with metastatic renal cell carcinoma was analyzed. Using a novel methodology for assessing efficacy, it was observed that sunitinib was not harmful, did not accelerate tumor growth and shorten the survival. Moreover, neither longer sunitinib treatment and nor a greater effect of sunitinib on tumors reduced the survival of metastatic renal cell carcinoma patients. The drug reduced tumor's growth rate and improved survival without appearing to negatively alter tumor biology after discontinuation. The results conclude that concerns arising from animal models do not apply to patients receiving sunitinib and likewise will not apply to patients using similar agents.

(Cell Reports, Feb 7, 2013)

CLINICAL TRIAL

Axitinib versus Sorafenib as Second-Line Treatment

A phase III clinical trial was conducted at Memorial Solan-Kettring Cancer Center to compare the efficacy and safety of axitinib versus sorafenib as a second-line treatment for metastatic renal cell carcinoma (mRCC). Researchers enrolled 723 patients randomly and distributed them (1:1) to receive axitinib (5mg twice daily n = 361) or sorafenib (400 mg twice daily n = 362). Primary end-point was progression free survival (PFS). Baseline charactersics and development of hypertension on treatmment were considered as prognostic factors. Findings revealed that median overall survival (OS) was 20.2 months and PFS 8.3 months with axitinib and OS was 19.2 and PFS was 5.7 months with sorafenib. In a post-hoc 12 week landmark analysis, median overall survival was longer in patients with diastolic pressure of 90 mm Hg or greater than in those with diastolic pressure less than 90 mm Hg in both the arms. Adverse events in both groups were hypertension, diarrohea, fatigue, and hand-foot syndrome. These findings show that axitinib is a better treatment option as a second-line treatment for patients with mRCC.

(Lancet Oncol, May 2013)

Everolimus in Metastatic Renal Cell Carinoma

A multicentric non-interventional study was done in Germany to evaluate the response of Everolimus in metastatic renal cell carcinoma (mRCC) patients after failure of initial vascular endothelial growth factor receptor- tyrosine kinase inhibitor (VEGFr-TKI). Primary end-point was effectiveness, defined as time to progression. Study documented records of 382 patients, though for analysis, 196 patients were included. Patients with previous treatment with VEGF targeted therapy for less then 6 months showed median time to progression (TTP) as 6.6 months, whereas patients who received it for more than 6 months, TTP was 7.4 months. In the efficacy population (n= 165) median TTP was 7.0 months. Adverse events were dysphnea (14%) and anemia (13%). Overall results showed that Everolimus is very effective and has shown extremely tolerance among patients.

(Oncologie, Feb, 2013)

Foretinib for Papillary Renal Cell Carinoma

Researchers at Dana-Farber Cancer Institute performed phase II trial to evaluate the efficacy and safety of foretinib in papillary renal cell carcinoma (PRCC). Foretinib is an oral multikinase inhibitor targeting various receptors including MET (Hepatocyte growth factor receptor) which has shown mutations or amplification in patients with PRCC. Total 74 patients were enroled in the study and were divided on the basis of MET pathway activation in two cohorts with 37 patients in each group. Cohort A received 240 mg once per day on day 1 through 5 every 14 days and cohort B received 80 mg daily. The primary end-point was overall response rate (ORR). According to the results, MET mutation was highly predictive of response. ORR was found to be 13.5% and median progression free-survival was 9.3 months as per the response evaluation criteria in solid tumors 1.0. Adverse events were fatigue, hypertension, gastrointestinal toxicities and non-fatal pulmonary emboli. Through this study, it was concluded that fortenib has high response rate with very less toxicity in patients of PRCC with germline mutation.

(J Clin Oncol, Jan 2013)

Peptide Vaccine for Metastatic Renal Cell Carcinoma

For the treatment of renal cell carcinoma (RCC) prime area of research is vaccination therapy as RCC is one of the most immunoresponsive cancer. A phase I, non-randmosied, open-label clinical trial was conducted at Kinki University, Japan, to evaluate the safety of vascular endothelial growth factor receptor 1 (VEGFR1) peptide vaccine in metastatic RCC patients. Data from 18 mRCC patients with cytokine-refractory and tyrosine kinase inhibitor (TKI) faliure were collected who have been treated with VEGFR1 vaccine. Assessment of clinical outcome was done using CT scan, magnetic resonance imaging or with x-ray examination in accordance with the WHO Response Evaluation Criteria in Solid Tumors. The primary end-point was the safety of vaccination. Of the 18 patients, 2 patients showed partial response during treatment, 8 patients had stable disease for more than 5 months with a median duration of 16.5 months. Adverse events were low grade headache, rashes. These results suggest that VEGFR1 peptide vaccine is safe and well tolerated. The observed clinical outcomes of the peptide vaccine were found to be very encouraging.

(Br J Cancer, Apr 2013)

WATCHOUT

Diagnosing and Monitoring RCC

Renal Cell Carcinoma (RCC) usually is detected incidentally by abdominal ultrasound (US) and computed tomography (CT). It is occasionally suggested by a radioisotope bone or renal perfusion scan. However, these techniques are time consuming and expensive. A number of efforts are currently performed to characterize RCC using molecular biological, cytogenetic, immunohistochemical as well as proteome-based techniques. In this context, many markers have been evaluated for their potential use as diagnostic or prognostic factors. However, as yet none of them has been validated in vigorous trials. Inventors Darbouret, Bruno et al of Cézanne S.A.S., France were awarded the European patent No. 1920256 in November 2012. This invention relates to a highly sensitive and specific in vitro method for the diagnosis of RCC based on the new finding that a selected metalloproteinase, namely MMP-7, and/or its physiological precursor, pro-MMP-7, are elevated in body fluids, especially serum or plasma, of RCC patients. The invention also relates to a specific ligand assay method for the detection of MMP-7 in a body fluid sample, i.e. the use of MMP-7 as humoral biomarker for RCC. *In vitro* method for diagnosing or monitoring renal cell carcinoma (RCC) in a human patient by determining in a sample of a body fluid of the patient a biomarker the level of which is indicative for the presence of RCC, and associating the level of the measured biomarker with the presence of RCC, wherein the biomarker is the metal containing peptide matrix metalloproteinase 7 (MMP-7) and/or its pro-enzyme form (pro-MMP-7) and is determined directly in a sample of a body fluid selected from serum, plasma and blood.

(www.patentslens.net; May 26 2013)

T-Cell Receptor Recognizing Renal Cell Carcinoma

US patent No. 8,431,690 has been assigned to Wang, et al. of The United States of America, as represented by the Secretary, Department of Health and Human Services (Washington,DC). The invention provides an isolated or purified T-cell receptor (TCR) having antigenic specificity for a cancer antigen, e.g., a renal cell carcinoma antigen, wherein the TCR recognizes the cancer antigen in a major histocompatibility complex (MHC)-independent manner. Also provided are related polypeptides, proteins, nucleic acids, recombinant expression vectors, isolated host cells, populations of cells, antibodies, or antigen binding portions thereof, and pharmaceutical compositions. The invention further provides a method of detecting the presence of cancer in a host and a method of treating or preventing cancer in a host using the inventive TCRs or related materials. This technology describes a T-cell receptor that was cloned from a human immune cell. This T-cell receptor recognizes a number of human kidney tumors and is not limited to use in patients with specific MHC types. This cell was able to kill other kidney cancer cells in other patients, and when this T-cell was introduced into other human immune cells, these cells also acquired the ability to kill kidney cancer cells. This invention also describes novel methods using dendritic cells to generate both CD4+ and CD8+ RCC- reactive T cells for use in antigen identification and therapeutic protocols. This is the first and only cloned T-cell receptor that recognizes a majority of human kidney tumors.

(www.uspto.org; Apr25 2013)

Treatment of Renal Cell Carcinoma

Inventors Jenny Nyström, Rosengatan et al of ONCORENA, Sweden, have been awarded the European Patent No. 2 349 268 on 16th March 2013. Cancer in the kidney constitutes about 3% of all solid tumors. About 85% of renal tumors are classified as renal cell carcinoma (RCC). Approximately 80% of diagnosed RCC originate from the epithelial cells lining the proximal parts of the kidneys' urine-forming ducts, the tubuli. Due to its appearance under the microscope, this cancer type is known as either renal clear cell carcinoma (RCCC, 65%) or renal papillary cell carcinoma (RPCC, 15%). While RCCC and RPCC constitute 80% of diagnosed RCC, they are responsible for close to 100% of the deaths from renal cell carcinoma. The present invention relates generally to cancer treatment. More specifically this invention relates to the use of 3,3',4,4'-tetrahydroxy-2,2'-bipyridine-N,N'-dioxides, for the treatment of renal cancer, particularly renal cell carcinoma originating from renal proximal tubular cells. It provides pharmaceutical compositions comprising pyridine-N-oxide and bipyridine-N,N-dioxide compounds for treating renal cancer by administering the pharmaceutical compositions to a patient suffering from or susceptible to renal cancer. The invention herein also includes a kit for treating a patient suffering from or susceptible to renal cancer.

(www.patentslens.net; May 10 2013)

GLOBE SCAN

Dyslipidemia and Renal Cell Carcinoma

Abnormal serum lipid profiles are associated with the risk of some cancers, but the direction and magnitude of the association with renal cell carcinoma is unclear. The authors explore the relationship between serum lipids and renal cell carcinoma via a matched case-control study. Cases (n = 248) were inpatients with a primary diagnosis of renal cell carcinoma, confirmed by pathology after operations. Controls were sampled from a community survey database matched on age and gender with cases, 2 controls for each case. Stratified Cox proportional hazard regression analysis was used to obtain hazard ratios and corresponding 95% confidence intervals of lipids level and dyslipidemia for the risk of renal cell carcinoma. Elevated serum cholesterol ($p<0.001$), LDL cholesterol ($p<0.001$), and HDL cholesterol ($p = 0.003$) are associated with decreased hazard of renal cell carcinoma, adjusting for obesity, smoke, hypertension and diabetes. This study indicates that abnormal lipid profile influences the risk of renal cell carcinoma.

(China; Plos One, Mar 2013)

Small Kidney Tumors

Small kidney tumors have an aggressive potential and should be treated, according to the results of a large multicentre study. The aim of this large retrospective multi-centre study was to evaluate the prevalence of locally advanced growth and distant metastases in patients with small renal cell carcinomas following surgery. The investigation included 2197 patients with RCC of 4 cm or smaller in maximal tumor diameter and complete patient and tumour specific characteristics. The risk of presenting nodal disease or distant metastasis increased insignificantly with rising tumor diameter. Patients with no lymphatic or distant metastasis at the time of diagnosis or surgery had a 5-year cancer specific death rate of 5.8%. 5-year cancer related death rate was significantly higher among the 75 patients with nodal or distant involvement at the time of surgery ($p<0.001$). In conclusion, the authors stress that lymph node and distant metastases occur even in small RCCs. These results have significant implications since the rate of patients diagnosed with small renal masses is increasing and non-operative surveillance protocols are currently being used in patients with small renal tumour.

(Germany; Science Daily, Mar 16, 2013)

BK Virus and Renal Cell Carcinoma

A study was done to investigate the potential association between the presence of BK virus (BKV) DNA and mRNA and renal cell carcinoma and bladder transitional cell carcinoma. The results of the nested PCR indicated that 23 (14.3%) of 160 samples were positive for BKV DNA. The relationship between the cancer and the presence of BKV DNA was significant ($P<0.05$). The BKV DNA positivity and significantly was associated with the histological diagnosis of renal cell carcinoma ($P=0.03$), but not with that of bladder transitional cell carcinoma. The results of real-time RT-PCR showed that mRNA of BKV VP1 was present in 69.5% of the BKV DNA positive samples. The levels of BKV mRNA were significantly higher in the renal cell cancer samples than in the control samples ($P<0.05$). The results of the present study confirm the association between BKV and renal cell cancer. The findings also indicated that the presence of BKV DNA resulted in a five fold increase in the risk of development of renal cell carcinoma.

(Turkey; J Med Virol, Jan 2013)

Fighting Kidney Cancer

Scientists have developed a compound that holds much promise in the laboratory in fighting renal (kidney) cancer. Named TIR-199, the compound targets the "proteasome," a cellular complex in kidney cancer cells, similar to the way the drug bortezomib targets and inhibits the proteasome in multiple myeloma cells. The novel feature of the new proteasome inhibitor, TIR-199, is that it is nearly as potent as bortezomib but is selective in inhibiting the growth of only renal cancer cell lines. The authors submitted TIR-199 samples to the National Cancer Institute, where the compound was subjected to a rigorous 60-cell screening used routinely to test compounds for their effectiveness in battling 60 kinds of cancer, including leukemia, lung, colon, brain, breast, ovarian prostate and renal cancers. The authors still have to fine-tune TIR-199 in the lab because some aspects–certain structural elements within it–make it easily metabolized,. But now that they have a good handle on how structural changes in the compound affect anticancer activity and how the parent drug binds to the proteasome, they are pretty confident of making a better version, the second generation of TIR-199.

(USA; ScienceDaily, Feb 19, 2013)

ACTIVITIES OF RGCI&RC

BREASTCON-2013 HIGHLIGHTS

The first ever international conference on early breast cancer **"BREASTCON 2013"** was organized by the Breast Services Department of Rajiv Gandhi Cancer Institute & Research Centre, Delhi. The theme of the conference was **Emerging Trends and Future Directions in the Management of Early Breast Cancer**. The conference was held in full grandeur and scientific fervour between 13th - 14th April, 2013 at India Habitat Centre, Lodhi Road, New Delhi.

Prof Robert Mansel, Head of Surgery, Cardiff University School of Medicine, UK, the man who pioneered the concept sentinel lymph node in the United Kingdom and steered the ALMANAC and the much awaited AMAROS trials delivered keynote addresses on topics most pertinent to India today "Accredition of Breast Centres". The other thought provoking concept of "Is there a future for breast surgery or will it be the technologist?"

Prof Ismail Jatoi, Professor & Chief - Surgical Oncology, University of Texas, San Antonio, USA, and a renowned breast surgeon, spoke on a contrarian perspective of mammographic screening. He also updated the audience on the current status and indications of MR mammogram and the implication of age on breast conservation.

Dr Amit Goyal, Consultant - Oncoplastic Breast Surgeon, Royal Derby Hospital, UK, showed his videos on 'Therapeutic Mammoplasty' and explained the technique in detail for the benefit of the younger surgeons. Dr Jayant Vaidya, Consultant Surgeon, Whittington Hospital, London, UK, introduced the concept of intraoperative radiation therapy (IORT) in the setting of Breast Conservation emphasized by the recent results of the TARGIT trial. Dr Christine Brezden Mansley, Medical Oncologist from the University of Toronto, Canada, gave an update on recent advances on targeted therapy in breast cancer.

Renowned National Faculty from all over the country presented valuable Indian data on the various aspects of management of early breast cancer. It was a feast to the minds to hear the stalwarts in the field of breast oncology, and to interact and argue with them to arrive at a consensus on the most burning issues in the purest of scientific spirit. The conference was tailored to cover recent advances in imaging, diagnostic dilemmas in in-situ cancers, optimal imaging for screening, diagnosis and treatment planning, role of genomic profiling techniques of breast conservation and reconstructive challenges, neoadjuvant strategies to optimize breast conservation, and adjuvant radiation and systemic therapy in the management of early breast cancer.

Inaugural Ceremony
(L to R: Mr Rakesh Chopra, Chairman, RGCI&RC; Mr D S Negi, CEO RGCI&RC; Dr DC Doval, Organizing Chairman BREASTCON-2013; Dr Kapil Kumar, Organizing Secretary, BREASTCON- 2013)

Scientific proceedings of BREASTCON- 2013)

The conference was attended by over 250 delegates from all over the country with great enthusiasm and about 50 students presented poster and oral papers in the competitive session. The panel discussions, and "Meet the Professor" session were well appreciated. Thus, the conference drew full houses from the minute it started till it ended in a fairy-tale note of All's well that ends well'.

(Dr Veda Padma Priya, Consultant; Dr Kapil Kumar, Sr Consultant, Dept of Surgical Oncology)

PERSONALIZED CANCER GENOME TEST FROM YALE SCHOOL OF MEDICINE–NOW AVAILABLE AT RGCI&RC

Over the past decade, since the decoding of the first human genome in 2003, a quiet revolution has taken place with the recognition that molecularly targeted therapies are most effective in patients whose tumors carry specific genetic or genomic alterations. Some of these changes in gene function contribute directly to neoplastic transformation and/or progression to full malignancy, and other changes modify the behavior of cells that have already become malignant. Many of these changes are alterations of DNA sequence, such as point mutations, insertions, deletions, amplifications, inversions, and chromosomal translocations.

In the personalized cancer treatment scenario, individual mutations within tumors are assayed to determine the likelihood of response or nonresponse to specific targeted therapies. This approach to predictive testing has been termed 'molecular tumor profiling'. Attention has shifted to high-throughput testing of tumors for dozens of predictive markers due to (a) the development of increasing numbers of molecularly targeted drugs, and (b) the alterations targeted by drugs found predominantly in certain types of cancer (or subtype) may be found with lower prevalence in a variety of other tumors. Overall, patient/tumor specific predictive marker analysis results in the identification of a mutation specific drug for the patient which has resulted in many more patients receiving only those drugs that are known to work for their kind of DNA mutation.

In collaboration with Precipio Diagnostics, RGCI&RC and Star Health Network, Inc are proud to offer the latest molecular tumor profiling tests for Lung, Breast, Biliary Tract, Ovarian, Acute Leukemia, Thyroid, Melanoma, Pancreas, Colorectal and Urinary Tract cancers. These tests, from the Yale School of Medicine, will be available in the very near future to RGCI&RC oncologists and their patients.

The Tumor Profiling Laboratory at Yale-New Haven Hospital is a CLIA-certified clinical facility that performs high throughput genotyping analyses of tumor DNA to predict the sensitivity or resistance of tumors to a variety of anti-neoplastic drugs. The overall aim of the laboratory is to provide oncologists with detailed mutational profiles of their patients' tumors so that treatment for patients may be individually optimized.

The laboratory isolates DNA from tissue samples containing tumor cells and analyzes specific sites within particular genes for the presence or absence of mutations. A total of 69 actionable mutations in 10 relevant genes are tested. An actionable mutation is one that is responsive to a currently approved drug or a new drug in clinical trials. For example, in non-small cell lung cancer (NSCLC), 9 genes (EGFR, KRAS, ERBB2, BRAF, PIK3CA, AKT-1, MEK-1, ALK and ROS) are tested for more than 48 actionable mutations. The more common mutations in EGFR and KRAS are responsive to Erlotinib and Gefitinib while there are clinical trials available for mutations in ERBB2, BRAF, PIK3CA, AKT-1, MEK-1, ALK and ROS.

No other gene/mutation panel has the following benefits:

- Relevance–Oncologists/patients receive a report that presents ONLY clinically-relevant information, focusing solely on 69 actionable mutations;
- Speed–Test results are provided within 10 days;
- Efficiency–Testing is managed through a staged and reflex protocol, ensuring that only relevant tests are conducted;
- Versatility - Diagnosis of any patient tissue from any type of organ; analysis is done on the smallest number of malignant cells, with virtually no specimen rejection.

Yale Tumor Profiling Lab – Comparative Analysis

This technology ensures that physicians receive consistent, quality reporting, and are capable of providing each patient with optimal, personalized care.

1. Actionable only diagnosis–analysis of mutations providing guidance relevant to patient treatment plan: (i) Mutations that indicate a responsiveness to drugs (ii) Mutations that indicate a lack of responsiveness to drugs.
2. Personalized–patient-tailored clinical trial and drug responsiveness information.
3. Expertise–diagnosis provided by MD/PhD pathologists from Yale School of Medicine.
4. Innovative–constantly updated gene/mutation panel as new drugs enter the market

About RGCI&RC and Star Health Network Partnership

Star is a New York City based company that has launched a global health network connecting centers of excellence in the United States to centers of need around the world. RGCI&RC recently signed a partnership agreement with Star that provides access to their network of US hospitals, their medical expertise and advanced care capabilities. Now, RGCI&RC and its network of physicians can offer their patients cutting edge testing, accurate diagnosis and expert opinion & consultation, based on the most current discovery– for every case.

BIOREPOSITORY

Rajiv Gandhi Cancer Institute and Research Center has established a world class Biorepository to meet the needs of scientific community focused on cancer research.

VISION

To have a contemporary "Biorepository"with all attributes necessary for good standing as enunciated by "International Society for Biological and Environmental Repository" (ISBER).

MISSION

To accelerate research by providing investigators access to large numbers of high quality biospecimens those are "annotated".

NABH NABL

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