

Renal cell carcinoma

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Purpose of review

Renal cell carcinoma continues to be a devastating cancer, which currently has few effective treatment options. Recent developments in our understanding of the molecular biology of renal cell carcinoma, particularly clear cell renal cell carcinoma, have led to the development of new agents targeting portions of the hypoxic response pathway.

Recent findings

Although high-dose bolus interleukin-2 remains the mainstay of treatment for metastatic disease, the number of patients deriving long-term benefit from this treatment are few, and the use of cytokine therapy in the adjuvant setting has been disappointing. However, the expanding use of minimally invasive surgical techniques has continued to improve patient care. Systemic advances include antibody therapeutics such as bevacizumab, which targets vascular endothelial growth factor signaling, as well as emerging small molecule inhibitors of angiogenesis-related signaling events.

Summary

In addition to progress in surgical techniques and supportive care of patients with renal cell carcinoma, a host of promising targeted therapies for renal cell carcinoma are on the horizon.

Keywords

renal cell carcinoma, vascular endothelial growth factor, von Hippel-Lindau

Curr Opin Oncol 16:247–252. © 2004 Lippincott Williams & Wilkins.

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Current Opinion in Oncology 2004, 16:247–252

Abbreviations

HIF	hypoxia inducible factor
IL	interleukin
RCC	renal cell carcinoma
VHL	von Hippel-Lindau tumor suppressor gene
TSC	tuberous sclerosis complex
VEGF	vascular endothelial growth factor

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1040-8746

Introduction

Renal cell carcinoma (RCC) has historically been a difficult malignancy that targets men and women primarily in the fifth and sixth decades of life, who if not candidates for definitive surgical resection are afforded little chance for long-term survival. The most recent data indicate that in 2003 an estimated 31,900 new cases of RCC were expected in the United States, with 11,900 deaths attributable to RCC [1]. Unlike many cancers, the National Cancer Institute reports a rising incidence of carcinoma of the kidney at a rate of approximately 2% per decade. Despite the discouraging statistics associated with RCC, this tumor type has been a fertile ground for recent advances in furthering our understanding of the molecular biology of tumorigenesis, as well as bringing biologically relevant treatments to clinical trials.

Molecular etiology

The von Hippel-Lindau tumor suppressor gene (VHL) is the most commonly mutated gene in human RCC. The VHL regulates the oxygen-dependent expression of genes implemented in the cellular response to oxygen deprivation. This includes the transcriptional activation of genes involved in angiogenesis, erythropoiesis, and anaerobic metabolism and is mediated by VHL interaction with the transcription factors hypoxia inducible factor (HIF)1 α and HIF2 α . VHL activity and the mechanism of hypoxic response regulation have recently been expertly reviewed elsewhere [2••]. Clear cell RCC with VHL mutation demonstrates constitutive HIF expression, and increased expression of HIF target genes, including vascular endothelial growth factor (VEGF) [3]. Recently, tremendous gains in our understanding of the hypoxic response pathway have led to a more thorough understanding of the molecular mechanisms that promote tumor growth in most clear cell RCCs, including angiogenesis, the glycolytic switch, and even the up-regulation of genes such as adipose differentiation related protein (ADRP), which mediate the influx of lipid, giving clear cell RCC its characteristic appearance [4•,5].

The tuberous sclerosis complex (TSC) is also a target for clear cell RCC in humans. Mutations in either of the tuberous sclerosis genes (TSC1, tuberin; and TSC2, hamartin) give rise to tuberous sclerosis disease, which carries a predisposition for the development of clear cell RCC. Mutation in TSC2 results in spontaneous RCC development in rodents [6]. TSC2 loss was recently shown to induce HIF1 α and HIF2 α expression, *via* the

mammalian target of rapamycin. Loss of TSC2 leads to the induction of the hypoxic response target gene, VEGF [7,8]. This mechanism of tumor promotion is remarkably similar to the dysregulation of the hypoxic response pathway observed in VHL-mediated human renal tumorigenesis, suggesting a common pathway in the development of clear cell RCC.

Although we continue to gain more precise levels of insight into the pathobiology of clear cell RCC, other histologic subtypes have a less well defined molecular fingerprint. Subtypes of RCC other than clear cell rarely have mutations in VHL or TSC2. Hereditary papillary RCC has been associated with mutations in the c-MET proto-oncogene; however, familial papillary-type II RCC, in patients with hereditary leiomyomatosis, was recently found to segregate with mutations in the fumarate hydratase gene, providing some of the first insight into the molecular biology of this subtype [9].

Prognosis and molecular biology

Several recent studies have attempted to identify prognostic markers of RCC. In comparison with other molecular lesions, clear cell RCC with disrupted VHL has demonstrated a better outcome in both disease progression and overall survival [10]. Tissue analysis of genes transcriptionally activated as a result of VHL mutation therefore has become an expanding area of investigation. The renal cell antigen G250 was recently identified as carbonic anhydrase IX (CA IX), a target of VHL disruption and the HIF transcriptional response by Bui *et al.* [11]. This study demonstrated an inverse correlation between CA IX expression and tumor stage, suggesting that it may serve as a surrogate for VHL status and an important prognostic marker. The expression of cyclooxygenase-2, a predictor of outcome in several other tumor types, was found in RCC to correlate with tumor proliferation, angiogenesis, and expression of matrix metalloproteinase-2, but expression levels did not correlate with survival [12]. Despite the recent advances in the molecular biology of RCC pathogenesis, several clinical features, such as collecting system invasion, continue to provide consistent prognostic information for RCC within the currently accepted staging strategies [13]. In clear cell RCC, the prognostic variables of tumor stage, regional lymph node status, tumor size, nuclear grade, and histologic evidence of necrosis all were statistically associated with progression to metastatic RCC and have been used to develop a scoring algorithm for predicting progression after nephrectomy for localized RCC [14]. As well, current evidence points to the number of metastatic sites as providing more prognostic value than the location of metastases [15]. Most evident is the difference observed in outcomes among the histologic subtypes of RCC. In one recent study, patients with clear cell RCC had a poorer prognosis than those with either papillary or sarcomatoid RCC, with survival rates at 5

years of 68.9% compared with 87.4% and 86.7%, respectively [16]. Additionally, an unclassified histologic subtype of RCC was recently described, which carries with it an extremely poor prognosis [17]. This observation in particular brings to the forefront of clinical cancer research the practice of including all histologic subtypes in clinical trials. As we gain understanding of the subtypes of RCC, it is becoming increasingly clear that the genetic changes underlying these subtypes of RCC are unique and well defined, and that recruitment of disease subtype specific treatments should be considered.

Several research groups have taken advantage of the increasing availability of the powerful technologies of array analysis and expression profiling to analyze RCCs for categorization of various aspects of this complex disease. cDNA microarray applied to RCC histologic subtyping reveals a strong correlation of gene expression with commonly practiced histologic identification, with the interesting exception that conventional clear cell RCC with granular cytoplasm had a surprisingly heterogeneous expression profile in comparison with other histologic subtypes of RCC [18]. Evaluation of tumor cell lines removes much of the heterogeneity of these studies, given that samples are cellularly and genetically more consistent; yet, the spectrum of the up-regulated genes in conventional RCC remains the same [19]. One particularly interesting observation was cKIT oncogene overexpression, detected by gene expression profiling in chromophobe RCC, which may suggest that the small molecule inhibitor of the KIT tyrosine kinase, imatinib, may have therapeutic value in this subset of patients [20]. Interestingly, an array approach to predicting survival identified unique sets of genes that did not correlate with histologic subtype or loss of the tumor suppressors VHL or TSC2 [21]. A sample of genes demonstrating increased expression is provided in Table 1.

Similarly, comparative genomic hybridization profiles showed concordance among conventional RCCs (each of 15 tumors showing loss of chromosome 3p), as well as papillary RCC (each of 13 tumors showing gains of chromosomes 7 and 17). In this analysis, comparison of comparative genomic hybridization diagnosis with histologic diagnosis was concordant in 41 of 42 samples, and additional studies confirm these findings [22,23] (Table 1). Additionally, tissue microarray has proved to be a useful tool for screening proteins across a large number of tumor samples, and it retains valuable histologic information in the data analysis [24,25]. Finally, emerging tools for proteomic analysis permit protein expression profiling, which can provide useful correlates for diagnosis, prognosis, and response to treatment [26]. A summary of findings from these new tools for cancer investigation is shown in Table 1. This evidence, taken together, further supports the paradigm that dysregulation of the hypoxic

Table 1. Tumor subtype analysis using array-based technologies

Renal carcinoma subtype	CGH analysis	cDNA expression array	Tissue microarray	Proteomics
Conventional (clear cell)	-3p ^a +5q ^a +7 ^a -8p ^b -9p ^b -14q ^b	VEGF ^a PECAM1 ^b Cyclin D1 ^b Glut-1, glut-3 Endothelin 1 EPAS1 (HIF2 α) PPAR γ TGF β 1 CA IX	Cyclin D1 Cyclin D3 p27 CA IX	Glycolytic enzymes ^b Annexin family ^b Vimentin ^b Cofilin 1 Elongation factor 2 Keratin 10 Thymidine phosphorylase
Conventional (granular) Papillary	N/A +7 ^b +17 ^b +16q ^b +3q ^b +12q ^b	Variable pattern Claudin family ^b Keratins 7, 17, 19 Plexin B1, GRO1, GRO2, Cathepsin C SRY-box 4 Villin 2	N/A Cyclin E p27	N/A N/A
Chromophobe	-1 ^b -2 ^b -6 ^b -10 ^B -13 ^b -17 ^b	KIT ^b SEC 4L RAB11A Fumarate hydratase PPARGC1 FOXO1A GADD45	Cyclin E	N/A
Oncocytoma	-1/1p, -14 Comparable to normal kidney	Same as chromophobe	N/A	N/A

^aObserved in three independent analyses. ^bObserved in two independent analyses. Data from Higgins *et al.* [18], Zatyka *et al.* [19], Yamazaki *et al.* [20], Wilhelm *et al.* [22], Junker *et al.* [23], Hedberg *et al.* [24], Unwin *et al.* [26], Seliger *et al.* [54], and Pavlovich *et al.* [63].

response pathway underlies the development of clear cell RCC.

Angiogenesis-targeted therapy

In keeping with the increasing molecular evidence for the role of the hypoxic response pathway and the attendant angiogenic response, attention has turned to targeting this pathway in the treatment of RCC. Perhaps the most noteworthy recent advance in the renal carcinoma field is the evidence supporting clinical efficacy of the use of an antibody targeting VEGF receptor activation, bevacizumab. A randomized phase II analysis of 116 patients demonstrated an improved time to progression in patients receiving bevacizumab when compared with treatment with placebo in metastatic disease (Fig. 1) [27••]. This study emphasizes the potential value of targeting angiogenesis and the hypoxic response pathway in this tumor type. A cancer and leukemia group (CALG)-sponsored randomized phase III trial of interferon- α *versus* interferon- α plus bevacizumab recently opened to accrual and should provide important information on the potential benefits of this treatment.

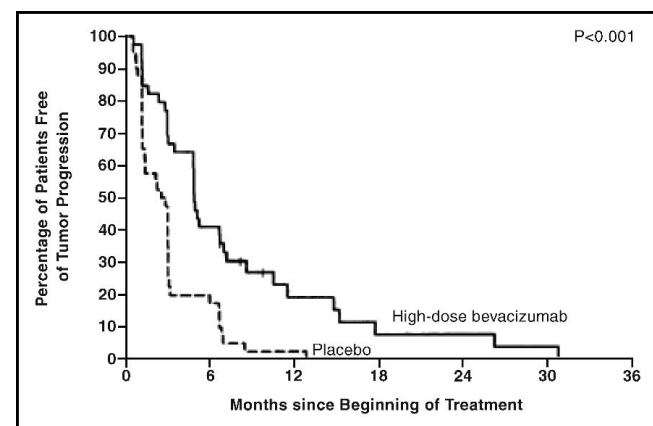
SU5416 is a small molecule inhibitor of the VEGF receptor pathway, which targets VEGF receptor 2, Flk-1. It is the first of what will likely be several small molecule alternatives to produce tumor antiangiogenesis. Although this agent has shown potent preclinical biologic activity and an impressive safety profile in phase I investigation, phase II studies have demonstrated a poor clinical response, which has diminished enthusiasm for

this agent [28–31]. Other small molecules, such as Bay 43-9006, with more promiscuous inhibition of tyrosine kinase-mediated signaling, have also shown promise in preclinical studies, and early-phase clinical trial evaluation is now being completed [32].

Surgical treatment

Nephrectomy remains the standard treatment for patients with all stages of disease. In the setting of advanced disease or metastasis, cytoreductive surgery has,

Figure 1. Kaplan-Meier analysis of survival free of tumor progression for patients receiving high-dose bevacizumab compared with placebo



Bevacizumab dosing was 10 mg per kilogram of body weight given every 2 weeks. *P* values were calculated by the log rank test. Reproduced from Yang *et al.* [27••] with permission.

for reasons that remain elusive, been effective in improving survival when combined with immunotherapy as initial treatment, although issues of patient selection and timing of therapy have generated some controversy regarding the effectiveness of this treatment [33–36].

The growing trend in clinical practice toward laparoscopic nephrectomy has gained support in the literature as an effective minimally invasive treatment of RCC. In a comparison of purely laparoscopic, hand-assisted laparoscopic, and open radical nephrectomy, both laparoscopic techniques were found to be safe and resulted in a decrease in pain medication and faster return to oral intake. Operative times, however, were similar in the three groups [37]. Specific groups of patients, in particular those with a high body mass index or other surgical contraindications, may have additional benefit from a laparoscopic procedure [38]. However, in an analysis of nephron-sparing procedures, laparoscopic partial nephrectomy was unfavorable compared with open partial nephrectomy in a single-institution analysis of 200 patients. The results demonstrated longer warm renal ischemia time, more major intraoperative complications, and more postoperative urologic complications, as well as a higher incidence of positive surgical margin in the laparoscopic group, suggesting that open nephrectomy remains the established standard for nephron-sparing interventions [39]. However, the emerging use of intraoperative imaging, particularly intraoperative ultrasonography, may permit the expanded use of laparoscopic procedures in a broader group of patients in the future [40].

Radiofrequency ablation

Radiofrequency ablation has recently found increased use in the evolving management of RCC. This minimally invasive therapy has gained a significant degree of enthusiasm for the treatment of patients with serious contraindications to nephrectomy, and early success as an intervention has prompted several promising retrospective institutional studies, including one in which 26 of 32 patients had successful primary ablation of tumors averaging 2.6 cm in size, and 5 of the remaining 8 patients were successfully ablated in a second session [41–44]. Radiofrequency ablation has great potential, especially in the treatment of multifocal nonbulky disease, as in patients with von Hippel-Lindau syndrome, and in the treatment of small renal masses in the elderly. However, prospective investigation of this modality must be performed before it enters widespread use to establish the tumor characteristics suitable for radiofrequency ablation, as well as the appropriate technical specifics of tumor localization and thermal delivery.

Chemotherapy

Continued investigations of chemotherapy, combined bio-chemotherapy, and intensified dosing strategies have undergone intensive scrutiny, recently analyzed in a de-

tailed overview by Sternberg and Vogelzang [45]. The most promising early studies of bio-chemotherapy used a combined regimen of 5-fluorouracil and immunotherapy [46,47]. However, subsequent trials using various dosing and delivery strategies for both the 5-fluorouracil and immunotherapy components have not shown an impressive pattern of response [48]. Gemcitabine-containing chemotherapy regimens have previously shown modest activity for treatment of relapsed disease [49]. This area of active investigation includes a recently completed trial of gemcitabine and capecitabine, with results that should be forthcoming. Interestingly, a recent study of irinotecan in metastatic RCC demonstrated a trend toward disease stabilization, particularly in the subgroup of patients who had previously received immunotherapy treatment [50]. Supportive care in the management of advanced disease remains particularly important in RCC. The use of zoledronic acid in patients with metastatic bone lesions leads to increased bone density and delayed development of meaningful skeletal-related events, and is a treatment modality that should not be overlooked [51].

Immunotherapy

High-dose bolus interleukin-2 (IL-2) remains the only therapy for advanced RCC approved by the United States Food and Drug Administration. The significant multisystem toxicity of this regimen, however, including a 1 to 4% treatment-related mortality rate, has led to the widespread use of low-dose regimens using outpatient administration of either IL-2, interferon- α , or a combination of the two. A randomized study recently compared high-dose IL-2 with low-dose IL-2 administered either intravenously or subcutaneously demonstrated an advantageous response rate for the high-dose regimen (overall response rate (ORR) for high-dose intravenous, low-dose intravenous, and low-dose subcutaneous achieving 21%, 11%, and 10%, respectively). Complete responses were observed in all treatment groups, with a trend toward more complete and durable responses in the high-dose group. Overall survival, however, was not significantly different in the three groups [52••]. Support for this highly toxic regimen, therefore, remains confined to the small population of patients who can achieve complete responses with durable remission. Pretreatment identification of this group of responding patients remains elusive, although HLA class II haplotype may be a predictive indicator of response [53]. Pretreatment classification of immunotherapy-responsive patients may be an ideal use of the expanding genomic and proteomic technologies [54]. Immunotherapy in the adjuvant setting has also been a topic of investigation, with disappointing results from recent Eastern Cooperative Oncology Group (ECOG)/Intergroup and Cytokine Working Group trials that demonstrated a poorer median survival and median recurrence-free survival in the arms treated with adjuvant interferon- α and IL-2, respectively [55•,56•].

Additional bio-immunotherapies have shown promise in the treatment of RCC, including IL-12 in combination with IL-2 [57•]. In particular, the emerging role of tumor-specific vaccination is a very active area of investigation. Vaccination strategies involving RCC-specific tumor antigens as well as those incorporating autologous whole tumor loaded dendritic cell vaccination strategies hold promise [58•,59,60]. Phase I data have demonstrated the safety of autologous vaccines while showing promising evidence of expansion of the T cell immune repertoire and unexpectedly low disease-related mortality [60–62]. These treatments remain limited to investigational use as studies under way determine the most useful type of vaccination, timing of vaccination, population of patients benefiting from vaccine, and the delivery method, as well as the clinical benefit in terms of time to progression or overall survival.

Future directions

Renal cell carcinoma is just beginning to see the therapeutic benefits of several years of very productive studies of the molecular biology of this disease. Clinical trials that use novel systemic therapies based on our emerging knowledge of the molecular dysregulation of the renal carcinoma disease subtypes will undoubtedly produce unprecedented enthusiasm for the treatment of renal cancers. Realistically high expectations exist for the further development of vaccine strategies for the treatment of high-risk patients with limited toxicity, as well as the rapid development of antiangiogenesis agents targeting endothelial growth signals or endothelial cell homeostasis. The preliminary results with bevacizumab provide an important proof of principle in the goal to molecularly define the disease and design unique therapeutic agents targeting the molecular mechanisms driving tumor growth. Finally, developing experience with minimally invasive treatments such as laparoscopic nephrectomy and radiofrequency ablation of renal tumors continues to improve the quality of care we can deliver to our patients without causing unnecessary morbidity.

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