Papillary Renal Cell Carcinoma: Current Progress and Future Directions

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Abstract

Papillary renal cell carcinoma (pRCC) represents the second most common histologic variant of kidney cancer. It exhibits a different molecular signature than clear-cell carcinoma and is typically not associated with mutations in the VHL (von Hippel-Lindau) tumor suppressor gene. pRCC is less responsive to modern drugs introduced in the management of kidney cancer in the past decade. In this article, the heredity and biology of 2 main variants of pRCC are outlined. New targets that are being explored in the treatment of this disease are discussed, with particular emphasis on inhibition of mesenchymal epithelial transition (*MET*) and epidermal growth factor receptor (EGFR) pathways. We discuss preclinical data providing rationale for the combination of *MET* and EGFR inhibitors and review recently completed and ongoing clinical trials that attempt to expand our therapeutic options for this important subset of kidney cancer.

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Introduction

The remarkable progress in the management of advanced kidney cancer over the past decade focused primarily on the most common histologic type-clear-cell carcinoma (ccRCC).[1] Less common histologic subtypes have been traditionally categorized as "non–clear-cell renal cell carcinoma" (nccRCC) and have been underrepresented in drug development efforts. Among these non–clear-cell subtypes is papillary renal cell carcinoma (pRCC), representing the second most common histologic subset of kidney cancer, accounting for approximately 15% of all incident cases. Among the non–clear-cell subtypes, pRCC constitutes approximately 50% of cases. In a recent analysis of the California Cancer Registry, pRCC comprised 64% of nccRCC.[2] In this database, patients with nccRCC tended to present at an early stage (93% were localized or regional) and therefore potentially curable with surgical therapy.

Pathology and Cytogenetics

The term pRCC is descriptive and reflects the presence of papillary architecture on histopathologic evaluation. Two distinctive morphologic types have been proposed: type 1 tumors have small cells with scanty pale cytoplasm arranged in a single layer on the basement membrane of papillary cores (Fig. 1). They frequently express cytokeratin 7. In contrast, type 2 tumors have cells that are larger (Fig. 2) and have pseudostratified nuclei and usually exhibit voluminous eosinophilic cytoplasm.[3]

Chromosomal and cytogenetic analyses have revealed gain of chromosomes 7 and 17, loss of Y chromosome, and additional gains (chromosome 3q, 8p, 12q, 16q, and 20q) in type 1 pRCC, but the chromosomal aberrations of type 2 pRCCs seem to be more heterogeneous.[4] Type 1 tumors appear to have better prognosis than type 2.[5]

Heredity and Biology

Papillary renal cell carcinoma (RCC) can present either as an inherited or sporadic malignancy. Two hereditary syndromes associated with pRCC have been described and are summarized in this section.

Hereditary papillary renal carcinoma (HRPC) is an autosomal dominant syndrome with high penetrance (90% probability of developing cancer by age 80 years).[6] Morphologically these tumors always belong to type 1 pRCC and are frequently multifocal. HRPC was linked to abnormalities at chromosome 7q31.3, and was subsequently associated with oncogenic activation of the mesenchymal epithelial transition (*MET*) gene.[7] *MET* is a proto-oncogene that encodes a cell surface receptor for ligand hepatocyte growth factor. Mutations in *MET* that result in constitutive activation of the tyrosine kinase domain lead to increased unregulated proliferation, invasion and metastases.

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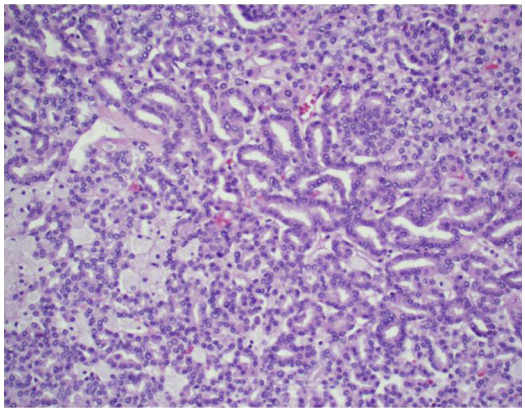
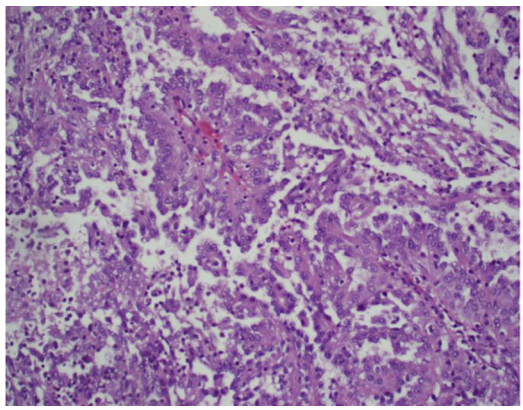
Figure 1 Type 1 Papillary Renal Cell Carcinoma



Hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome is associated with cutaneous and uterine leiomyomatomas and in approximately 20% of cases with pRCC, predominantly of type 2 morphology.[8] In contrast to other forms of hereditary kidney cancer, HLRCC-associated renal tumors are typically solitary and unilateral but their nuclear grade is high (Furhman 3-4) and prognosis poor.[9] Genetic alterations associated with HLRCC were mapped to chromosome 1q42.3-q43 and correspond to the fumarate hydratase (*FH*) gene. *FH* is an enzyme in the Krebs cycle that catalyzes the conversion of fumarate to malate. Biallelic inactivation is detected in virtually all HLRCC cancers, indicating that *FH* is a tumor suppressor gene.[10] It appears that intracellular accumulation of fumarate leads to stabilization of hypoxia-inducible factor-1 alpha and increased production of vascular endothelial growth factor (VEGF) in a manner somewhat analogous to pathophysiology of clear-cell RCC, although via a different underlying molecular mechanism.[11]

Although germ line *MET* proto-oncogene mutations are the hallmark of HRPC, somatic *MET* mutations in sporadic pRCC occur in only 5% to 13% of cases.[12] However, most patients with sporadic type 1 pRCC harbor duplication of chromosome 7, or amplification of the region where *MET* is located, indicating a likely alternative mechanism for *MET* activation in sporadic pRCC.[7,12] In sporadic type 2 pRCC, somatic *FH* mutations are rare and the molecular abnormalities are very heterogeneous.[13]

Figure 2 Type 2 Papillary Renal Cell Carcinoma



Recent Clinical Developments

Although the treatment of advanced ccRCC has undergone dramatic changes with the introduction of mammalian target of rapamycin (M-TOR) inhibitors, and tyrosine kinase inhibitors of VEGF receptor (VEGFR) and its relatives, optimal management of pRCC and other non–clear-cell histologies remain undefined. There have been few published clinical trials specifically evaluating the effects of these compounds in pRCC.

The analysis of clinical trials that allowed treatment of multiple RCC histologies provides some insight into their efficacy in pRCC.

Vascular Endothelial Growth Factor Pathway Inhibitors

In an expanded access trial of sunitinib in RCC, 588 patients (13% of total) with non–clear-cell histologies were identified. Most of them had previous cytokine therapy. Unfortunately, this trial did not differentiate between the different non–clear-cell subtypes, but based on prevalence it is likely that pRCC constituted a significant fraction of these patients. A response rate of 11% and median progression-free survival (PFS) of 7.8 months were noted.[14] A small phase II trial of sunitinib in patients with nccRCC enrolled 26 patients (including 13 (50%) patients with pRCC). There were no objective responses and median PFS was 48 days.[15] Choueiri et al reported on the efficacy of sunitinib and sorafenib in metastatic nccRCC.[16] This retrospective analysis identified 53 patients who had been treated with either sunitinib or sorafenib at 5 different cancer centers in the United States and France. The number of patients with pRCC was 41 (77%), of which 23 had received previous systemic therapy (non-VEGF targeted). Of the 41 patients with pRCC, 13 were treated with sunitinib. Response rate was 15% and median PFS was 7.6 months. In a subset analysis, patients with pRCC treated with sunitinib had the longest median PFS of 11.9 months (compared with 5.1 months if treated with sorafenib $P < .001$).

In an expanded access trial of sorafenib in advanced RCC, 158 of 2504 patients (6.4%) were classified as pRCC. Response rate in this subgroup was only 3% and PFS was not reported.[17] A subset of patients (13%) participating in the AVOREN (Phase III Trial of Bevacizumab Plus Interferon Alfa-2A versus interferon Alfa-2A monotherapy in Patients With Metastatic Renal Cell Carcinoma) trial that established the role of combination of bevacizumab (bev) and interferon-α 2A (IFN) in the management of RCC exhibited mixed histology including the pRCC component. These patients demonstrated overall inferior PFS than patients with pure clear-cell histology but they also benefited from combination bev/IFN over IFN alone, demonstrated by increased PFS (5.7 vs. 2.9 months).[18]

Mammalian Target of Rapamycin Inhibitors

Temsirolimus was evaluated in previously untreated patients with metastatic RCC and unfavorable clinical characteristics.[19] This