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Systemic Therapy for Metastatic Non-Clear Cell Renal Cell Carcinoma: Recent Progress and Future Directions

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Abstract

Renal cell carcinoma (RCC) encompasses a heterogeneous group of histological subtypes of which clear-cell RCC (CCRCC) is the most common comprising more than 70–80% of all cases. Papillary renal cell carcinoma (PRCC) is the next most common comprising 10–15% of cases. PRCC is refractory to chemotherapy, immunotherapy and hormonal therapy.

Insights into the biology of clear-cell RCC have identified multiple pathways associated with the pathogenesis and progression of this cancer. This has led to the development of multiple agents targeting these pathways including the small molecule tyrosine kinase inhibitors sorafenib, sunitinib and pazopanib, the monoclonal antibody bevacizumab and the mTOR inhibitors temsirolimus and everolimus. These drugs have shown significant clinical benefits in randomised trials in advanced CCRCC and have become the standard of care for most patients. With the exception of temsirolimus, phase III trials tested these agents in patients with clear-cell histology, and therefore, their efficacy in non-clear cell RCC is unclear. To date, there is no established effective therapy for patients with advanced non-clear cell RCC (NCCRCC). This review will focus on the treatment options of metastatic NCCRCC.

Keywords

non-clear cell renal cell carcinoma; VEGF; mTOR; targeted therapy; papillary; chromophobe; unclassified; renal medullary carcinoma; collecting duct carcinoma; sarcomatoid dedifferentiation

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Introduction

Renal cell carcinoma (RCC) affects more than 40,000 patients in the United States each year[1]. Localised disease is curable with surgery but a significant proportion of patients relapse or present with metastatic disease that is largely incurable[2–4]. Until relatively recently all adult renal epithelial tumours were labelled as “renal cell carcinomas” or “Kidney Cancers”. Over the last 15 years renal cell carcinoma has increasingly been recognised as a heterogeneous disease with several distinct subtypes that have differing clinical, pathological and molecular characteristics.

Renal cell carcinomas can be divided into clear cell (CCRCC, 70–80%), and non-clear cell (NCCRCC) histologies. The latter one mainly include: papillary (PRCC, 10%–15%), chromophobe (ChRCC, 5%), unclassified (5%), collecting duct and medullary (CDRCC, MRCC, <5%)[5]. In the era of immunotherapy, metastatic CCRCC was perceived to have a better outcome than PRCC [6, 7] but this has been contradicted by a large study of 1,001 patients with metastatic RCC (82 of which had PRCC), showing similar 5-year survival rates of around 10% irrespective of clear cell or papillary histology [4]. ChRCC is acknowledged to have the best overall prognosis compared to other subtypes, in both local and metastatic disease, and the same study confirmed this, indicating 5 year survival rates of 87.9% in ChRCC compared to 73.2% in CCRCC.

In the past decade, various targeted therapies such as tyrosine kinase inhibitors (TKIs), mammalian target of rapamycin (mTOR) inhibitors and VEGF monoclonal antibodies have changed the paradigm of CCRCC management. However, a key unresolved issue is whether these therapies can replicate their efficacy in NCCRCC. Indeed, most clinical trials to date have focused on patients with clear cell histology. Retrospective analysis of these trials has indicated potential activity of targeted agents in NCCRCC, and as such, prospective trials have been initiated. This review will outline the different subtypes of NCCRCC, as well as the latest therapeutic developments in NCCRCC.

Development of Targeted Agents

Improved understanding of the molecular biology underlying RCC has led to the development of several drugs that specifically target distinct pathways, and there is now convincing evidence that they are of benefit in patients with clear cell histology [8, 9]. This raises the question of whether VEGF is a valid target in NCCRCC. Despite the fact that VHL inactivation and the subsequent overexpression of hypoxia-inducible genes such as VEGF are hallmarks of CCRCC, patients with papillary, chromophobe and medullary histology can still demonstrate high expression of VEGF, VEGFR-1 and VEGFR-2 (especially in more advanced stages) that is correlated with worse survival, making VEGF-targeted therapy an attractive therapeutic option [10, 11,12,13]. There are currently two major classes of targeted agents of particular interest for treatment of NCCRCC.

Tyrosine kinase inhibitors

Kinase inhibitors are drugs that generally inhibit tyrosine kinase (TK) enzymes which catalyze the transfer of phosphate groups from adenosine triphosphate (ATP) to tyrosine

residues on proteins [14]. This can be an activating event for proteins involved in signalling and leads to increased cellular proliferation and the promotion of angiogenesis and metastasis. Receptor tyrosine kinases (RTKs) such as the epidermal growth factor receptor (EGFR) are located in the cell membrane and transduce signals from the extracellular environment to the cell interior [14]. Numerous downstream signalling pathways such as RAS/RAF/MEK/ERK and PI3K (phosphoinositol 3′-kinase)/Akt may be activated by ligand binding to a RTK [15]. Non-receptor tyrosine kinases such as c-ABL are located intracellularly and can be activated by mechanisms such as phosphorylation. TKIs disrupt TK signalling by preventing the binding of either protein substrates or ATP [14], and examples of TKIs with activity in NCCRCC include sunitinib, sorafenib, erlotinib and pazopanib.

mTOR inhibitors

mTOR is a non-receptor serine/threonine kinase in the PI3K-Akt pathway that controls the translation of specific messenger RNA; mTOR activation has multiple downstream effects including increasing HIF-1α gene expression [16]. Furthermore, reduced PTEN expression has been demonstrated in some renal cell carcinomas [17, 18] and loss of PTEN function results in Akt phosphorylation with downstream effects on cell growth and proliferation that may be blocked using rapamycin derivatives [19]. There is therefore a strong rationale for using mTOR inhibitors in RCC.

Sporadic PRCC

Pathology and molecular biology

Sporadic PRCC is itself a heterogeneous entity with at least 2 and possibly 3 distinct subtypes, both at the morphological and genetic levels that appear to have different clinical characteristics [5, 2021]. As might be expected, most of these tumours have a papillary, tubular, or tubulo-papillary growth pattern.

From a histological standpoint, two different subtypes of papillary renal cell carcinoma (PRCC) are identified, type 1 with small cells and pale cytoplasm and type 2 with large cells and eosinophilic cytoplasm [2022]. Similarly, these two subtypes have distinct cytogenetic and molecular profiles that distinguish them from other renal epithelial tumours. Although only about 10% of sporadic type I PRCC have been reported to show somatic mutations in the c-MET gene, a genetic abnormality commonly seen as a germline mutation in hereditary cases [23], the c-*Met* pathway can be activated in many sporadic PRCC in the absence of c-*Met* mutation [24]. The group from the National Institutes of Health described the genetic abnormality associated with the hereditary form of the type 2 papillary RCC, consisting of mutations in the fumarate hydratase (*FH*) gene [25]. The contribution of this mutation to the pathogenesis of sporadic papillary type 2 RCC remains unknown.

More recently, Yang and colleagues proposed a refinement of the former (type I/Type II) classification and introduced a molecular classification [21]. Using gene expression profiling, they identified two highly distinct molecular PRCC subclasses with morphologic correlation. The first class, with excellent survival, corresponded to three histologic subtypes: type 1, low-grade type 2, and mixed type 1/low-grade type 2 tumours. The second

class, with poor survival, corresponded to high-grade type 2 tumours. Dysregulation of G1-S and G2-M checkpoint genes were found in class 1 and 2 tumours, respectively. c-met was differentially expressed, with higher expression in class 1 tumours. This refined classification of PRCC based on morphological and molecular characteristics may be more relevant and is likely to aid diagnosis, prognosis, treatment and analysis of clinical trials in advanced papillary RCC.

Treatment

Sunitinib inhibits the RTKs VEGFR2, PDGFR, FLT-3 and c-KIT [26, 27] (Table 1). A dose of 50mg orally once a day for 4 weeks followed by a 2-week break was the recommended phase II dose based on 2 phase I studies [28, 298, 29]. It has subsequently been shown to significantly increase progression free survival in patients with metastatic CCRCC and has become a first-line standard of care for these patients [9].

A Worldwide expanded access trial of sunitinib has been undertaken, with a primary purpose to make the drug available to patients before regulatory approval. More than 4,000 patients have been enrolled into this study giving an important database especially for subgroup analysis. In May 2007, Gore and colleagues presented data on 2,341 patients, the majority of whom (78%) had received prior cytokine therapy [30]. A subgroup analysis of patients with non-clear histology was performed and 276 patients (11.8%) with non-clear histology were identified, although distinction between different subtypes was not made. A response rate of 5.4%, clinical benefit (defined as response and stable disease >3 months) of 47% and median PFS of 6.7 months was seen in this subgroup. This compared with an overall response rate for the entire patient group of 9.3%, clinical benefit of 52.3% and median PFS of 8.9 months. The authors concluded that sunitinib was active in the non-clear cell subgroup, however this data needs to be interpreted with caution due to the non-randomisation of patients in the expanded access trial, and lack of pathology verification.

In light of the results of the retrospective subgroup analysis, further trials have been initiated in order to provide additional data on sunitinib activity in NCCRCC. In 2008, Plimack and colleagues reported preliminary results from a phase II study of sunitinib in patients with NCCRCC – in a cohort of 26 patients of whom 13 had PRCC, there were no objective responses, although 8 patients did experience stable disease [31]. Moreover the response rate and median PFS (48 days) were disappointing. Recently, updated results from this trial have been reported [32]. The trial has been expanded to include 48 patients, with analysis focused on the patients with PRCC (23). Unfortunately, results remained disappointing – amongst the PRCC patients the median PFS was 1.6 months (95% CI, 1.3–12), the median OS was 10.8 months (95% CI, 6.2-NE), and no major responses were observed, with the best response being stable disease (seen in 8 patients).

The SUPAP study is another phase II trial investigating sunitinib activity in type 1 and 2 PRCC [33]. 28 patients were enrolled, and of the 23 patients with type 2 PRCC, one had a partial response, and 13 had stable disease (lasting for ≥12 weeks in 4 patients). 5 patients had type 1 PRCC, and although none experienced a partial response, 3 had stable disease. Based on these results, the authors concluded that sunitinib did have some activity in PRCC, albeit inferior compared to CCRCC.

These conclusions have been supported by the results of another phase II study conducted in a cohort of 23 NCCRCC patients by Molina and colleagues [34]. There were 8 patients with PRCC, and in this subgroup no partial responses were seen, with a median PFS of 5.6 months (95% CI, 1.4–7.1). The data from recent phase II studies has therefore tempered the initial optimism raised by the retrospective subgroup analysis, and it appears that sunitinib at best has modest activity in PRCC. Nevertheless, there are still several ongoing phase II trials investigating sunitinib therapy for PRCC, and their results will be useful in clarifying the role of sunitinib in NCCRCC (NCT00465179, NCT01034878 and NCT01219751). One study of 9 patients from Korea was preliminarily presented at the 2011 Genitourinary Cancers Symposium and showed a response rate of 38% and a time to progression of 6.4 months. The authors considered the primary endpoint has been met and suggested that sunitinib has promising activity in patients with NCCRCC [94].

Sorafenib inhibits the RTKs VEGFR2, VEGFR3, Flt-3, c-KIT and PDGFR and the non-receptor serine threonine kinases BRAF and CRAF [35] (Table 1). The BRAF and CRAF kinases are members of the RAF/MEK/ERK signalling cascade, which is involved in the survival and proliferation of tumour cells and is a therapeutic target in cancer [36] although it is not known to be of major importance in RCC. Sorafenib has subsequently been shown to significantly increase progression-free survival in patients with metastatic CCRCC who had progressed on cytokine therapy and is licensed for the treatment of metastatic RCC [8].

Ratain and colleagues were among the first to administer sorafenib to metastatic PRCC[37]. In a phase II randomised discontinuation study; they treated 15 PRCC patients out of a total of 202 patients. From this subgroup, 2 patients achieved a partial response and 3 patients had tumour shrinkage of 25–49%; this was comparable to the entire population and indicated sorafenib activity in PRCC.

In one of the largest detailed series to date, Choueiri and colleagues reported on the efficacy of sunitinib and sorafenib in metastatic papillary and chromophobe RCC[38]. This retrospective analysis identified 53 patients who had been treated with either sunitinib or sorafenib at 5 different cancer centres in the US and France. In contrast to the expanded access studies, expert genitourinary pathologists from each institution reviewed the cases to confirm the histopathological diagnosis of NCCRCC. 41 patients had PRCC; 13 were treated with sunitinib and of these, 2 patients achieved a partial response (15% response rate), with durations of 12 months and 8+ months. No responses were seen in the 28 patients treated with sorafenib. In total, 27 patients (68%) achieved stable disease for more than 3 months after 2 cycles of treatment with sunitinib or sorafenib. Minor responses ranging from −4% to −25% were seen in 9 patients. PRCC patients had a PFS of 7.6 months, and it was observed that treatment with sunitinib resulted in a superior PFS compared to sorafenib (PFS 11.9 vs. 5.1 months, respectively $p < 0.001$), and this remained statistically significant even after adjusting for other important prognostic factors in metastatic RCC such as hemoglobin and the number of metastatic sites.

A Worldwide expanded access trial of sorafenib has also been undertaken. Response data on the Advanced Renal Cell Carcinoma Sorafenib (ARCCS) expanded access trial in North America has recently been reported on 1,891 patients out of a total of 2,504 patients

enrolled [39]. This study contained a subgroup of 107 PRCC patients with valid data. Within this subgroup, 3 patients (3%) exhibited partial responses, with 87 patients (81%) experiencing stable disease lasting for at least 8 weeks. This study also included an extension protocol for which NCCRCC patients and patients who had not received prior therapy were eligible, although specific distinctions between NCCRCC subtypes were not made. Data was available for 248 patients in this extension protocol; NCCRCC patients (n=26) had a PFS of 46 weeks (95% CI, 30–59; censorship rate 39%) compared to first-line patients who had a PFS of 36 weeks (95% CI, 33–45; censorship rate 56%). Overall in the whole trial, toxicities for NCCRCC patients did not differ from those seen in patients with CCRCC, and sorafenib was well tolerated in both groups. Moreover, it was concluded that sorafenib appeared to have activity against PRCC.

A similar European expanded access study of sorafenib was undertaken (the European ARCCS) [40]. This included 118 patients with PRCC of whom 104 were evaluable for response. The disease control rate was 66.4% and the median PFS was 5.8 months for PRCC compared to 75.7% and 7.5 months for patients with CCRCC respectively.

Overall, currently available data from retrospective and expanded access studies suggests that sorafenib may possess activity against PRCC. Smaller scale studies have also supported this impression. Unnithan and colleagues investigated cell lines established from primary and metastatic tumours from a patient with type II PRCC, and reported that sorafenib inhibited cell growth and expression of angiogenic genes such as VEGF and PDGF [41]. Given its apparent promising activity, further trials may be necessary to confirm whether sorafenib is suitable for NCCRCC therapy.

Temsirolimus, a derivative of sirolimus (rapamycin), inhibits mTOR (Table 1). Temsirolimus has been studied in a 3 arm phase III study comparing temsirolimus, interferon alpha (IFN-α) and the combination of the 2 agents as first-line therapy for poor-risk patients with metastatic RCC [42]. Response rates were similar in all 3 arms and ranged between 7–11% but median overall survival was longer in the temsirolimus single agent arm in comparison with the other 2 arms (10.9 months for temsirolimus, 7.3 months for IFN-α and 8.4 months for the combination; hazard ratio 0.73, p=0.0069 for single agent temsirolimus). The authors concluded that temsirolimus as a single agent significantly improves overall survival of patients with metastatic RCC and poor-risk features as compared with IFN-α but the combination of the 2 drugs does not improve overall survival.

In this study, approximately 20% of all patients had non-clear cell histology. Of these patients, 75% had PRCC. A subset analysis has been performed to determine the effect of temsirolimus versus IFN-α on OS and PFS in patients with clear-cell or other histologies[43]. For NCCRCC patients (n=73), those in the temsirolimus group had a longer OS and PFS than those in the IFN-α group (median OS 11.6 vs. 4.3 months, respectively; HR 0.49; median PFS 7.0 vs. 1.8 months, respectively; HR 0.38). Thus, it seems that temsirolimus may benefit patients irrespective of histology and warrants further study in patients with non-clear cell histologies. Unfortunately, this study had no central review of the histology and therefore there was no detailed differentiation between different non-clear cell subtypes.

More recently, Yang and colleagues performed further retrospective analysis, focusing on quality of life (QoL) data gathered using the EuroQoL-5D utility score (EQ-5D index) and EQ-5D visual analogue scale (EQ-VAS) [44]. It was observed that the mean EQ-5D score was higher in the temsirolimus arm compared to the IFN-α arm in NCCRCC patients.

The possibility that mTOR inhibitors have clinical activity regardless of RCC histology has led to the development of studies aimed at patients with non-clear histology, and a phase II trial comparing temsirolimus against sunitinib as first-line therapies is currently recruiting. (NCT 00979966) Everolimus is another mTOR inhibitor that is being investigated by several trials. Most notably, the RAPTOR study aims to evaluate everolimus as a first-line therapy for PRCC. (NCT 00688753) Other ongoing trials are also investigating the use of everolimus alone, or in comparison to sunitinib, for treatment of NCCRCC. (NCT 00830895, NCT 01185366, NCT 01108445). The randomised phase II studies comparing mTOR inhibitors versus sunitinib may help to clarify the relative role of each agent in NCCRCC.

The rationale for the use of erlotinib, an oral EGFR TKI, in PRCC stems from a study by Perera and colleagues. They demonstrated that blockade of the epidermal growth factor receptor (EGFR) by an anti-EGFR monoclonal antibody resulted in significant growth inhibition in non-clear cell RCC-derived cell lines, suggesting that EGFR blockade may provide a potential therapeutic approach [45]. In a study led by the Southwest Oncology Group (SWOG), Gordon and colleagues treated 45 patients with PRCC with erlotinib (150 mg/day). Five patients achieved a PR for an overall response rate of 11% (95% CI, 3–24) with a disease control rate (DCR) of 64% (5 PR + 24 stable) [46]. Median overall survival time was 27 months (95% CI, 13–36 months). There was no correlation between EGFR expression and disease outcome, and the drug was generally well tolerated. Although the RECIST response rate of 11% did not exceed pre-specified estimates (≥ 20% response rate) for further study, single-agent erlotinib yielded encouraging DCR and OS results. As a result of its promising activity, 2 phase II trials are now underway in order to investigate erlotinib alone and in combination with bevacizumab in patients with PRCC. (NCT 01130519, NCT 00060307)

Foretinib (GSK1363089) is a novel inhibitor of receptor tyrosine kinases targeting MET and VEGFR. In a phase I study partial responses were noted in 2 out of 4 patients with PRCC, lasting for longer than 48 and 12 months [47]. This has led to the initiation of a multi-center phase II study of foretinib (240 mg/day PO for 5 days on/9 days off) in patients with histologically confirmed PRCC [48]. After enrollment, patients were stratified into two strata based on the presence or absence of a genetic aberration in c-MET (A: evidence of c-MET pathway activation; B: without evidence of activation). 31 patients were enrolled (15 strata A and 16 strata B), and of 25 evaluable pts, 24 had at least stable disease and 20 had decreases in tumor size (range 4–35%). Two pts had confirmed PR and two had unconfirmed PR pending independent confirmation. The same trial has expanded to investigate the efficacy and safety of two dosing regimens (240mg 5 days-on/ 9 days-off vs. 80mg daily) of foretinib for PRCC [49]. Of 37 enrolled patients in the 5-on/ 9-off cohort, 35 were evaluable; 4 patients experienced confirmed partial responses and 27 had stable disease. Enrolment is incomplete in cohort 2, however, among 9 evaluable patients, 2 had

partial responses and 7 had stable disease. The authors concluded that foretinib was well tolerated and displayed promising anti-tumour activity. Therefore, it appears that foretinib may be an effective therapy of PRCC. The final results from this study are eagerly awaited.

Pathology and molecular biology of ChRCC

Pathology and molecular biology

Chromophobe renal cell carcinoma (ChRCC) is a subtype of renal cell carcinoma (RCC) distinguished from clear-cell RCC and other forms of non-clear RCC, by a distinct set of clinicopathological and molecular features. ChRCC arises from renal intercalated cells and can be divided into 3 subtypes – classic, eosinophilic and mixed. All subtypes are characterized by a sheet-like histological appearance, and vary depending on whether they possess a pale or eosinophilic cytoplasm. ChRCC was first identified by Bannasch et al in experimental renal tumor models in rats [50]. These tumors arose in the rat model after exposure to nitrosomorpholine, and had a characteristic cloudy cytoplasm. Similar neoplasms were later found in humans by Thoenes et al [51]. The World Health Organization (WHO) classification recognized ChRCC as a distinct subset of RCC in 2004.

Epidemiologically, ChRCC makes up about 4% of RCC. It is most often diagnosed in the 6th decade of life, but may occur more frequently in younger patients than other forms of RCC. Unlike other forms of RCC, male-to-female ratio is approximately equal. ChRCC like other forms of RCC is most often found incidentally on imaging. Radiographically, ChRCC are typically hypovascular tumors which compress the renal vasculature, and usually have a homogenous appearance. Pathologically, ChRCC tumors tend to be beige uniform masses which lack necrosis and hemorrhage [52].

Genetically, ChRCC cells tend to be hypodyploid, and often feature loss of heterozygosity involving chromosomes 1, 3p, 6, 10, 13, 17 and 21 [53]. In addition, ChRCC is a feature of Birt-Hogg-Dube (BHD) syndrome. This autosomal dominant condition involves mutations in the *BHD* gene, resulting in benign cutaneous tumours, RCCs (especially with chromophobe histology) and spontaneous pneumothoraces. *BHD* encodes folliculin, a tumour suppressor, and it has been reported that *BHD* is also mutated in sporadic ChRCC [54].

Deranged expression of the receptor tyrosine kinase KIT is also understood to be important in ChRCC. *KIT* is an oncogene involved in several cell processes including proliferation, apoptosis and differentiation, and is known to be abnormally activated in various neoplasias. Gene expression analysis has indicated upregulated expression of KIT on ChRCC cell membranes, and therefore KIT may prove to be useful for the diagnosis and treatment of ChRCC [55]. Mutations or rearrangements of mitochondrial DNA have been frequently observed [56]. mRNA expression profiles in ChRCC are quite similar to those in oncocytomas, with ChRCC expressing more distal nephron markers. This observation suggests that ChRCC and oncocytoma may represent spectrums of differentiation from the same progenitor cells, and both are thought to be derived from intercalated cells of the collecting duct system. Both ChRCC and oncocytomas occur with increased frequency in patients with Birt-Hogg-Dube (BHD) Syndrome, providing further evidence of the relatedness of these two tumors.

Treatment

Some of the aforementioned data described for PRCC is also applicable to ChRCC, since many trials have not distinguished between specific NCCRCC subtypes. Examples include the retrospective analysis of the sunitinib expanded access trial as well as the Phase III temsirolimus trial. Both trials included ChRCC patients, but no definite conclusions can be drawn since the data did not differentiate between the different subtypes of NCCRCC.

In the retrospective study by Choueiri and colleagues on sunitinib and sorafenib in NCCRCC,[38], 12 of 53 patients had ChRCC. Of these, 7 were treated with sunitinib and 5 with sorafenib. Partial responses were seen in 1 patient treated with sunitinib, and 2 patients with sorafenib, and the remaining 9 patients all experienced stable disease for at least 3 months. The median PFS time for sorafenib-treated patients was 27.5 months, and although both agents had activity, the low patient number precluded any firm conclusions to be drawn.

The ARCCS expanded access trial of sorafenib has also yielded valuable data on ChRCC patients. This cohort of 202 patients contained 20 ChRCC patients with available response data. No complete responses were seen, although 1 patient (5%) did have a partial response, and 17 patients (75%) had stable disease for longer than 8 weeks. Both studies therefore indicate potential activity for targeted agents in ChRCC, and as such several trials are underway (Table 2).

Recent data has also pointed to a possible role for chemotherapy in treatment of ChRCC. Capecitabine is a fluoropyrimidine, which is converted into 5-fluorouracil (5-FU). 5-FU has shown activity in metastatic RCC when combined with IL-2 and interferon, and consequently a phase II study has been conducted investigating capecitabine and docetaxel in metastatic RCC [57]. In a cohort of 25 patients, 10 patients (40%) experienced stable disease (90% CI, 25–58). Of interest, most of the patients with prolonged stable disease had non-clear histology, including one patient with ChRCC. A phase II trial evaluating capecitabine in metastatic NCCRCC has since completed accrual of patients, with results yet to be published. (NCT 01182142)

Pathology and molecular biology of renal medullary carcinoma

Renal medullary carcinoma (RMC) is a newly recognized aggressive form of kidney cancer, which was first described in a case series by Davis in 1995 [58]. All patients in the series were less than 40 years old, black, and nearly all had sickle cell trait. This new entity was quickly designated the seventh sickle cell nephropathy (the other six are: gross hematuria, papillary necrosis, nephrotic syndrome, renal infarction, inability to concentrate urine, and pyelonephritis) [59].

Since the original report, over 150 additional cases have been reported, and clear clinical and epidemiological associations noted in the original report have been confirmed. Patients diagnosed with RMC tend to be young (median age around 30 years), almost always of black race (although Hispanic/Brazilian and even a few Caucasian patients have been reported), and virtually all have sickle cell trait or sickle cell disease. A male/female ratio of

2:1 has been observed in adults, although in children the male predominance in even greater. The clinical presentation of RMC varies, but nearly all patients are symptomatic at diagnosis. Pain and hematuria are the most commonly seen symptoms. The right kidney is more often (>75%) affected than the left [60, 61].

Pathologically, the tumors are malignant epithelial tumors, which arise from collecting duct epithelium. They tend to be solitary, gray–white masses with macroscopic necrosis and hemorrhage. [62, 63].

Clinically, renal medullary carcinomas tend to be highly aggressive. Metastases to the lymph nodes, liver, and lungs are common at diagnosis. Treatment has proved challenging, as neither chemotherapy nor radiation therapy has been found to be particularly useful in this disease. Tannir et al presented a series of 22 patients with RMC from four major institutions at the 2011 Genitourinary Cancer Symposium. The authors of this study found that targeted therapy has low efficacy when given as monotherapy. They noted that currently cytotoxic chemotherapy is the mainstay of treatment, but this modality provides only modest short-term palliation, with median survival of about one year from diagnosis [64]. Albadine et al performed immuno-expression analyses of tissues, and found that topoisomerase II alpha was overexpressed in 11 of 13 (85%) cases, suggesting that this might be an appropriate target of therapy [65]. Schaeffer et al reported results of whole-genome expression of four RMC tumors that showed increases of topoisomerase II in all cases. They further reported a case of metastatic RMC in which a complete response was achieved for 9 months using topoisomerase II-inhibitor therapy [66].

Genetically, the loss of INI1, a factor in the ATP-dependent chromatin-modifying complex, is seen in some renal medullary carcinoma as well as renal rhabdoid tumors. The absence of INI1 expression does not appear to be predictive of rhabdoid histopathology, but is associated with aggressive behavior in renal medullary carcinoma [67]. Rearrangement of the ALK receptor tyrosine kinase has been reported in renal medullary carcinoma, as well. Marino-Enriquez et al identified a novel ALK oncoprotein in which the cytoskeletal protein vinculin (VCL) was fused to the ALK kinase domain in a case of RMC harboring a t(2;10) (p23; q22) translocation. Their report suggests a rationale for studying the treatment of RMC with targeted ALK inhibitors [68].

Although rare, RMC has garnered interest among oncologists, as well as physicians who treat sickle cell disease. There are currently no open clinical trials aimed solely at RMC, but a handful of trials seek to enroll patients with various forms of non-clear cell kidney cancer. As the molecular drivers of RMC are further elucidated in the laboratory, new treatment options should emerge.

Pathology and molecular biology of CDRCC

Pathology and molecular biology

CDRCC (also known as Bellini’s tumor) is rare and arises from the collecting ducts. By light microscopy, CDRCC is indistinguishable from RMC. Due to its rarity, little data exists, although it is known that CDRCC is genetically similar to urothelial cancers [69].

Treatment

One of the largest trials focusing on CDRCC to date was conducted in 2007. This phase II study enrolled 23 patients, and investigated treatment with gemcitabine combined with either cisplatin or carboplatin. Results were encouraging, with median PFS of 7.1 months (95% CI, 3–11.3) and OS of 10.5 months (95% CI, 3.8–17.1). One patient experienced a complete response.

More recent data has further pointed to a potential benefit of chemotherapy in this type of cancer. Bortezomib is a proteasome inhibitor which acts to interfere with degradation of cell cycle proteins, as well as with the expression of genes involved in angiogenesis and metastasis. Phase I trials confirmed the safety of the drug, as well as indicating potential benefit for treatment of RCC [70]. This data prompted a phase II trial which enrolled 37 patients with metastatic disease, with doses of 1.5mg/m^2 given to 25 patients, and 1.3mg/m^2 given to 12 patients [71]. Partial responses were seen in 4 patients (11%; 95% CI, 3–25) and stable disease in 14 patients (38%; 95% CI, 23–55). Notably, of the 4 patients with responses, one had RMC. Ronnen and colleagues have since reported that after 7 months of treatment with bortezomib, this patient achieved a complete response, and was disease free for 27 months at the time of writing [72]. Therefore, bortezomib may have a role in the treatment of RMC/CDRCC. Further data is required to assess its activity. One phase II trial of bortezomib in NCCRCC has completed accrual and results are awaited with interest. (NCT 00276614)

Given the rarity of both CDRCC and RMC, very few patients with either histology were treated with targeted therapy. Ansari and colleagues reported a patient with metastatic CDRCC who was treated with sorafenib, resulting in PFS exceeding 13 months [73]. Clearly, further data is necessary to characterise treatments for CDRCC and RMC, and this is being addressed in ongoing trials (Table 2).

Uncommon Types of NCCRCC

Mucinous tubular and spindle-cell carcinoma (MTSCC) is a recently described type of renal cell carcinoma thought to arise from either the collecting duct or loop of Henle. MTSCC is characterized histologically by the presence of tubules, spindle – cells, and mucinous stroma. MTSCC is associated with a 4:1 female predominance. Multiple chromosome losses have been identified in MTSCC. Some studies have shown trisomies of chromosome 7 and 17. The majority of these tumors follow an indolent course, although there are a few case reports of lymph node and visceral metastases[74,75]. Rarely, MTSCC may be associated with sarcomatoid dedifferentiation and carries a poor prognosis.

Tubulocystic carcinoma is another recently described type of NCCRCC, with a strong male predominance (7:1). It is histologically distinguished by the presence of tightly packed tubules and interspersed cysts. On electron microscopy, abundant microvilli with a brush border resembling proximal convoluted tubules can be seen. Other cells resembling intercalated cells of the collecting duct may also be seen. Genetic studies suggest some relationship to papillary carcinoma. Metastases have been reported in a few cases [76]. Sunitinib showed a response in a patient who failed 2 lines of cytotoxic chemotherapy.[95]

Renal translocation carcinomas are rare tumors often found in children or young adults. They almost exclusively are associated with translocations involving a transcription factor, E3 located on Xp11.2, although other chromosomal translocations have been described. Confirmation of the presence of a translocation, either by immunohistochemical, genetic, or molecular methods is required for diagnosis. These tumors tend to present at advanced stages but often have a relatively indolent course,[77,78,79] especially in children and adolescents. There is a female preponderance, with the vast majority of patients having lymph node metastasis at presentation [80, 81] Translocation carcinoma of the kidney responds less well to targeted therapy than CCRCC, but partial responses are seen with sunitinib and other anti-VEGF agents[80, 81].

Thyroid-like or follicular renal carcinoma represents a rare and newly emerging form of kidney cancer reported in only a handful of cases. Histologically, these tumors are distinguished by the presence of a pseudo-capsule and micro and macro-follicles. Of the few cases reported, all patients remained tumor free following surgery [82]. However, a recent case report described a patient who presented with lung and retroperitoneal lymph node metastases at initial diagnosis[83].

Sarcomatoid features in RCC

Sarcomatoid features is likely a more appropriate nomenclature than “sarcomatoid RCC”, since these features can be seen with all types of RCC. The presence of sarcomatoid dedifferentiation is now understood to reflect a final common pathway that can occur in diverse tumor types. It is associated with high grade, aggressive tumors and short survival. The estimated median survival for patients with localized disease is 17 months, and for patients with metastatic disease only 7 months [84].

Patients with metastatic sarcomatoid RCC do not appear to benefit from cytoreductive nephrectomy. In most cases, the sarcomatoid features are only identified after the nephrectomy [85]. In a single-institution series of 417 patients who underwent cytoreductive nephrectomy at UCLA [86], the median overall survival for 62 patients with sarcomatoid RCC was 4.9 months, compared to 17.7 months for those without sarcomatoid features. Patients identified as having sarcomatoid RCC prior to cytoreductive nephrectomy might benefit from immediate systemic therapy rather than surgery.

There is currently no standard therapy for metastatic or unresectable sarcomatoid carcinoma of the kidney, and there are very few published clinical studies. In a retrospective study, Golshayan et al [87] reported the median time to progression and median overall survival of 43 patients with sarcomatoid RCC treated with VEGF-targeted agents. There were 8 objective responses (19%), median time to progression was 5.3 months, and median OS was 11.8 months. Patients who had CCRCC as the underlying epithelial component and 20% or less sarcomatoid elements had better outcome. In the only published phase II clinical trial in sarcomatoid RCC, the regimen of doxorubicin and ifosfamide produced no objective responses, with median time to progression of 2.2 months and median overall survival of 3.9 months[88]. Experience with the combination of doxorubicin and gemcitabine given every 2 weeks with granulocyte-colony stimulating factor (G-CSF) support in metastatic RCC was

reported[89]. Among the 10 patients with sarcomatoid RCC treated in that series, two had complete responses and one patient had a partial response. Two of the patients with complete responses were subsequently reported to be have survived 6 years and 8 years; both of these patients initially had a local tumor recurrence in the renal bed[90]. Based on these preliminary observations, a phase II clinical trial (ECOG 8802; Clinicaltrials.gov identifier NCT00068393) of doxorubicin and gemcitabine in metastatic sarcomatoid RCC is in progress. Preliminary results from ECOG 8802, reported in abstract form, suggested an overall response rate of 16%, median overall survival 8.8 months, and progression-free survival 3.5 months[91]. Single-arm phase II trials are currently evaluating the role of chemotherapy and VEGF-targeted agents given in combination [92, 93].

Conclusion

Recently, there have been considerable advances in the understanding of CCRCC. These have been translated into the development of several drugs with improved efficacy, of which, the kinase inhibitors have demonstrated the most significant activity. Initial studies of these drugs have shown promising activity in metastatic NCCRCC, and additional prospective studies of these and other agents are needed. Several such studies are open to recruitment or planned and their results will help to define the role of these drugs in the management of NCCRCC. Further work is being done to understand the pathogenesis of this NCRCC and it is hoped that this will lead to a situation where treatment can be optimized for each individual patient.

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Table 1

Selected Targeted Agents Demonstrating Activity in Papillary Renal Cell Carcinoma.

Agent	Target
Sorafenib	**VEGFR2, VEGFR3, PDGFR, FLT-3, c-KIT, CRAF, wtBRAF, V600E BRAF**
Sunitinib	**VEGFR2, PDGFR, FLT-3, c-KIT**
Temsirolimus	**mTOR**
Erlotinib	**EGFR**
Foretinib (GSK1363089) (previously XL880)	**MET, VEGFR2**

VEGFR = vascular endothelial growth factor receptor; PDGFR = platelet-derived growth factor receptor; VEGF = vascular endothelial growth factor; mTOR = mammalian target of rapamycin; EGFR = Epidermal growth factor receptor; MET = Mesenchymal epithelial transition factor.

Table 2

Targeted agents currently under evaluation in selected clinical trials

Agent	Subtype	Trial number
Sunitinib	Metastatic NCCRCC (all types)	NCT 00465179
	Metastatic NCCRCC (all types)	NCT 01034878
	Metastatic PRCC, ChRCC, MRCC	NCT 01219751
Temsirolimus versus sunitinib	Locally advanced and metastatic NCCRCC (all types)	NCT 00979966
Everolimus	Metastatic PRCC	NCT 00688753
	Metastatic NCCRCC (all types)	NCT 00830895
Everolimus versus sunitinib	Metastatic PRCC, ChRCC, CDRCC	NCT 01185366
	Metastatic PRCC, ChRCC	NCT 01108445
Erlotinib	Local and metastatic PRCC	NCT 00060307
Erlotinib and bevacizumab	Hereditary and sporadic metastatic PRCC	NCT 01130519