Advanced Treatments in Non-Clear Renal Cell Carcinoma

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Purpose: To focus on the use of targeted therapies against the non-clear histologic subtypes of renal cell carcinoma (RCC); papillary I and II, chromophobe, and collecting duct. The unique genetic and molecular profiles of each distinct non-clear kidney cancer subtype will be described, as these differences are integral to the development and effectiveness of the novel agents used to treat them.

Materials and Methods: On the basis of MEDLINE database searches, we assessed all aspects of targeted therapy in non-clear cell RCC between 2000 and 2010. Trials focusing on non-clear RCC or those that treated clear cell tumors along with significant numbers of non-clear subtypes will be discussed. The role of cytoreductive nephrectomy and the use of neoadjuvant and adjuvant targeted therapy will be reviewed. Lastly, areas of future research will be highlighted.

Results: The majority of clinical trials testing novel targeted therapies have excluded non-clear subtypes, providing limited therapeutic options for patients with these diagnoses and their oncologists.

Conclusion: Patients presenting with advanced non-clear pathology should undergo a thorough metastatic evaluation and, if appropriate, surgical evaluation to determine if nephrectomy, lymphadenectomy, and/or metastectomy are warranted. Aggressive surgical extirpation is often recommended. Sunitinib also is adequately tolerated and oncologically active in subjects with non-clear histology.

Keywords: kidney neoplasms, renal cell carcinoma, classification, mortality

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INTRODUCTION

Background

Renal cell carcinoma (RCC) is among the most common adult malignancies in the United States, ranking fifth in men and eighth in women, with approximately 57 760 new cases diagnosed in 2009.[1] Renal cell carcinoma is not a homogenous entity and a number of malignant histologic subtypes, such as clear cell, papillary, chromophobe, and collecting duct, are recognized by the Heidelberg classification system (Figure).[2] Each RCC subtype is associated with unique genetic alterations, clinical characteristics, and sensitivity to treatment.[3-5]

The systemic management of advanced and metastatic RCC has drastically altered over the past 5 years with the approval of a number of targeted agents, supplanting cytokine-based therapies as the treatment of

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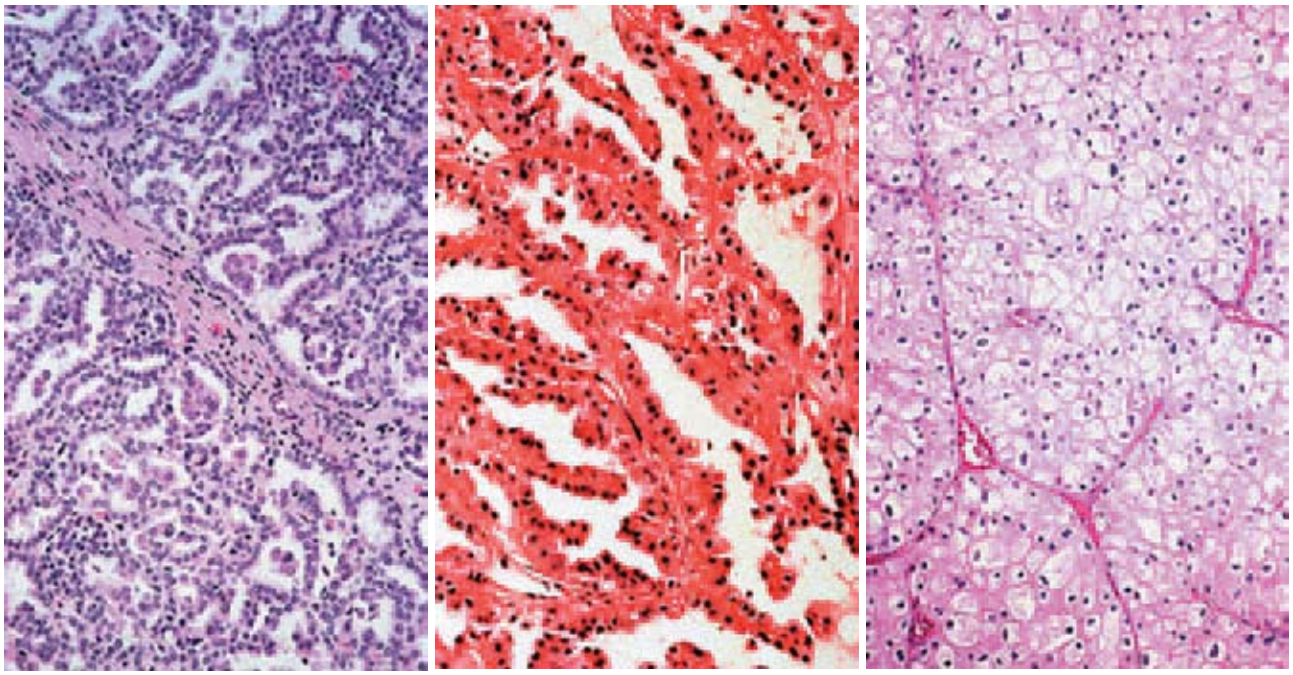

Papillary type I
5%

Papillary type II
10%

Chromophobe
5%

Histopathologically distinct non-clear renal epithelial neoplasms and their incidence.

choice for the majority of patients with clear cell RCC.[6-8] Despite these advances, the optimal treatment for patients with non-clear histologies remains undefined. This review will discuss the genetic and molecular biology of papillary, chromophobe, and collecting duct RCC and the targeted therapeutic strategies being employed to treat them.

Clear cell RCC, which is the most common histologic subtype of RCC and accounts for approximately 75% of the kidney cancer diagnoses,[9] provides the paradigm for translational research that takes bench top basic science to bedside therapies. Mutations in the von Hippel-Lindau (VHL) gene, which is located on the short arm of chromosome 3 and serves as an autosomal dominant tumor suppressor, were identified by studying patients afflicted with hereditary and sporadic clear cell kidney cancer.[4,10,11] Targeting the downstream transcriptional products resulting from mutational inactivation of the VHL gene, which are involved in angiogenesis and cellular proliferation and include vascular endothelial growth factor (VEGF), transforming growth factor α (TGFα), and platelet-derived growth factor β (PDGFβ),[12] allowed novel agents, such as sunitinib,[11] sorafenib,[13] and temsirolimus,[14] to be introduced against a disease that is notoriously resistant to cytotoxic chemotherapy and radiotherapy.[15] While these agents mark a major advance in the treatment of clear cell RCC, nearly every trial in which they were tested excluded the other subtypes of RCC, providing clinicians and their patients little guidance when selecting a systemic treatment for non-clear cell RCC. Fortunately, the same methodology of studying the genetic and molecular characteristics of hereditary and sporadic non-clear cell RCC tumors has identified promising new pathways that are amenable to targeted therapy.[5]

Objective

The primary aim of this review is to assess the development of targeted systemic therapies.

This review will focus on the use of targeted therapies against the non-clear histologic subtypes of renal cell carcinoma; papillary I and II, chromophobe, and collecting duct.

MATERIALS AND METHODS

Search Strategy

On the basis of MEDLINE database searches, we assessed all aspects of "targeted therapies in non-clear cell carcinoma" between February 2000 and December 2010. Seventy-two articles were found to detail future strategies to understund and treat non-clear cell carcinoma on the basis of evolution in targeted therapies.

RESULTS

Papillary Renal Cell Carcinoma

Papillary RCC is the second most common histologic subtype of the kidney cancer, accounting for approximately 10% to 15% of cases and nearly 29% of all RCCs in African Americans.[9,16] It can be further categorized histologically into papillary types I and II. Emerging data suggests that there may be significant differences in the genetics and molecular pathways underlying different types of papillary RCC as well as disparate outcomes associated with these entities.[17] Researchers and clinicians must take these differences into account when they design targeted therapies and treatment protocols for patients with papillary RCC.

Papillary type I RCC, in both the sporadic and hereditary forms, is associated with activating mutations of the methyl-nitroso-nitroguanidine-induced (MET) oncogene on the long arm of chromosome 7.[18] These mutations result in ligand-independent activation of intracytoplasmic tyrosine kinase domains, which constitutively activate the hepatocyte growth factor/MET pathway.[19,20] Families with hereditary papillary renal cancer harbor germline mutations in MET, usually accompanied by non-random duplication of the chromosome 7 bearing the mutated MET allele. Mutated MET is passed to offspring in an autosomal dominant fashion with variable penetrance. Phenotypically, patients with this gain of function germline mutation display bilateral multifocal papillary type I renal tumors.[20] Activated somatic MET mutations have also been identified in the tumors of patients with sporadic papillary type I RCC. While one study identified mutations in 13% of patients with all subtypes of non-familial papillary RCC, the prevalence of this genetic alteration in sporadic type I papillary RCC has not been adequately defined.[21]

Papillary type II tumors are now recognized as a distinct entity and occur both sporadically and in patients who have the familial syndrome of hereditary leiomyomatosis and renal cell carcinoma (HLRCC).[22] The genetic alteration associated with HLRCC has been localized to chromosome 1 and the gene identified as fumarate hydratase (FH). Fumarate hydratase functions as a classic tumor suppressor, with both copies inactivated in tumors. The mutation is transmitted in an autosomal dominant pattern with high penetrance.[23] Patients with HLRCC are at risk for the development of papillary RCC. These tumors have characteristic large orangeophilic nuclei and a clear perinuclear halo, with a variety of architectural patterns, such as papillary, tubulo-papillary, tubular, solid, or mixed.[24] Fumarate hydratase is a tricarboxylic acid (Krebs) cycle enzyme that plays a crucial role in aerobic cellular metabolism.[25] One well-described consequence of FH inactivation is the generation of a pseudo-hypoxic state, characterized by the upregulation of hypoxia-inducible factors (HIF), similar to that seen in the VHL pathway, albeit by a different mechanism.

Isaacs and colleagues demonstrated that inactivation of FH and consequent accumulation of its substrate, fumarate, lead to inhibition of HIF prolyl hydroxylase (HPH), a critical enzymatic regulator of intracellular HIF levels, through competitive inhibition.[25] Inactivation of HPH interferes with hydroxylation of HIF at key proline residues and its subsequent recognition by the VHL complex; thus, preventing VHL-dependent proteosomal degradation of HIFs. The resulting accumulation of HIF leads to transcriptional overexpression of proangiogenic factors, such as VEGF, as well as other genes, such as TGF-α, PDGF, and glucose transport (GLUT-1). In essence, this is an example of VHL-independent HIF accumulation in fumarate hydratase deficient kidney cancer, resulting in increased amounts of proangiogenic and growth

factors.[25] There is currently no well-described sporadic counterpart to HLRCC-associated kidney cancer and no conclusive evidence that somatic FH mutations play a significant role in sporadic kidney cancer tumorigenesis. However, the role of mutations in FH and other Krebs cycle enzymes, such as succinate dehydrogenase in the genesis of sporadic papillary RCC, is under evaluation.

Localized papillary RCC, which can be managed with surgical excision, has a more favorable prognosis than conventional clear cell.[26,27] However, metastatic papillary RCC portends a worse prognosis.[28] Few trials have focused their attention on papillary RCC as the primary histologic tumor type; therefore, the majority of data available is from expanded access trials, retrospective studies, and subset analyses with the inherent limitations these methods imply.

The Advanced Renal Cell Carcinoma Sorafenib Expanded Access Program allowed patients in the United States and Canada with metastatic RCC to receive treatment with sorafenib prior to its regulatory approval. This non-randomized, open-label program treated 158 subjects with papillary RCC of a total of 1891 evaluable subjects (81% clear cell, 8% non-clear, and 11% unclassified histology).[29] Of the 107 evaluable subjects with papillary RCC, 90 (84%) had a measurable response to treatment with 3 partial responders and 87 with stable disease for at least 8 weeks, while 17 (16%) subjects demonstrated early progression on treatment. The side effect profile for sorafenib was similar across histologic subtypes, and the authors concluded that sorafenib has some activity in papillary tumors.

Gore and associates treated 588 subjects with non-clear histology (not further subclassified) in their multi-center, international, non-randomized, expanded access compassionate use trial examining the safety and efficacy of sunitinib.[30] Of these, 437 were evaluable; however, the trial did not predefine criteria for measuring response, which was instead determined according to local practice. A total of 48 (11%) subjects had an objective response (46 partial responses and 2 complete responses), while 250 (57%) had stable disease for 3 months. Nearly one-third of the subjects (n = 139; 32%) progressed within 3 months. Despite focusing on poor-prognosis populations that were typically excluded from other trials because of the presence of brain metastases, Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2, age ≥ 65 years, or non-clear histology, the safety profile of sunitinib was similar to that seen in traditional patient populations.[11,31-33] The median overall survival (OS) for subjects with non-clear RCC in this study was 13.4 months, which is an improvement over the historical control of 9.4 months (a historical control was used given the non-randomized design of this trial).[34] The lower overall response rate (11%) for the non-clear histology group may have been influenced by the lack of a protocol-mandated evaluation procedure and the dependence on local standards of care to measure changes in disease burden.[30] Despite this limitation, the authors concluded that sunitinib is adequately tolerated and oncologically active in poor-prognosis populations, including subjects with non-clear histology, and that its use and further study are appropriate.

Choueiri and coworkers reported their retrospective multi-center review of 41 subjects with metastatic papillary RCC, who were treated with either sunitinib or sorafenib in the United States and France, which represents one of the largest papillary-only series published to date.[35] They found that although response rates were low (5% overall, 17% for sunitinib group), progression-free survival (PFS) was longer in those treated with sunitinib rather than sorafenib (11.9 months versus 5.1 months; $P < .001$). While the number of subjects in this retrospective analysis was small and the overall response rate was low, the PFS in patients treated with sunitinib is similar to that published for subjects with clear cell histology,[12] suggesting some activity for this agent. Unfortunately, there was no stratification of subjects based on papillary I versus II subtypes, which may indicate that the natural history and aggressiveness of these two entities were not adequately controlled in this trial.

In contrast, a recent report from Plimack and colleagues of their phase II experience with sunitinib in 23 patients with advanced papillary

RCC outlines the minimal activity associated with this drug and underscores the need to look beyond single agent VEGF pathway antagonists.[36] No objective responses were seen in this prospective, single-arm study. Eight patients had stable disease as their best response with a median PFS of only 1.6 months and median OS of 10.6 months. Similarly, Ravaud and associates from the French Genito-Urinary Group and the Group of Early Phase Trials examined sunitinib as a first-line therapy in subjects with locally advanced or metastatic papillary RCC in their on-going phase II trial. Their preliminary data on 5 subjects with papillary I and 23 subjects with papillary II RCC found no papillary I responders and only 1 papillary II partial response.[37]

Hudes and coworkers also included a significant number of subjects with non-clear histology in their Global Advanced RCC Trial comparing temsirolimus, interferon alfa, or both for advanced RCC.[14] This international, multi-center, randomized phase III trial treated a total of 626 subjects with poor-prognosis metastatic RCC. One hundred and twenty-four (20%) subjects were classified as having non-clear cell RCC. However, a central pathology review was not performed and further subclassification was not provided. Subjects of all histologic types receiving temsirolimus monotherapy had a median OS of 10.9 months, compared to 7.3 and 8.4 months for the groups receiving interferon alfa alone or temsirolimus plus interferon, respectively. Likewise, median PFS times were 5.5, 3.1, and 4.7 months, respectively, using Response Evaluation Criteria in Solid Tumor (RECIST) completed by independent radiologists. Hazard ratios for OS among the non-clear RCC subgroup also favored treatment with temsirolimus over interferon alfa. Subsequent exploratory subset analyses based on tumor histology from Global Advanced RCC determined that 55 subjects had papillary RCC and that those in the temsirolimus group (n = 25) had prolonged OS (11.6 versus 4.3 months, respectively) and PFS (7.0 versus 1.8 months, respectively) compared to those treated with interferon alfa (n = 30).[38] Although these data represent an exploratory subset analysis, this report is significant in that temsirolimus is the only agent approved by the Food and Drug Administration for advanced RCC that has been evaluated in non-clear cell RCC in a phase III trial. These data suggest that mammalian target of rapamycin (mTOR) inhibitors, either as single agents or in combination, should be further evaluated in papillary RCC in prospective studies.

A prospective phase II trial of everolimus, an oral mTOR inhibitor, as monotherapy in advanced papillary RCC, is ongoing in Europe. Foretinib (also known as GSK1363089 or XL880) is an oral receptor tyrosine kinase inhibitor (TKI) that targets c-MET and VEGFR2 and has been studied in a phase II multi-center trial.[39] Two different dosing regimens, a daily and an intermittent dosing regimen, were evaluated in this trial. Interim data on the first 60 patients (37 in the intermittent dosing arm and 23 in the daily dosing cohort) were reported recently in abstract form. Response Evaluation Criteria in Solid Tumor partial responses were seen in 7/53 evaluable patients, including 4/37 or 11% of patients receiving intermittent dosing and 3/16 or 19% of patients on the daily dosing regimen. In addition, over 70% of patients treated had stable disease, with the majority demonstrating some degree of tumor shrinkage. The drug was well-tolerated, with a side effect profile akin to that seen with other VEGF receptor antagonists. The trial has completed accrual and final efficacy analysis is awaited. Foretinib is the first MET antagonist to be evaluated in papillary RCC and patients will be retrospectively stratified based on c-MET status to determine if clinical efficacy is correlated with MET activation.

Erlotinib is an oral epidermal growth factor receptor tyrosine kinase inhibitor. A multi-center phase II trial of this agent in patients with locally advanced and metastatic papillary RCC reported an overall RECIST response rate of 11% (5/45 patients) with an additional 24 (53%) patients experiencing stable disease.[40] The 6-month PFS was only 29%; however, the median OS was 27 months. Although this was a single-arm, uncontrolled study, the OS reported was higher than that has been reported for patients with metastatic papillary RCC.[34,35] Addition of mTOR inhibitors or VEGF pathway

antagonists may potentiate the single agent activity of erlotinib. A phase II trial of erlotinib in combination with bevacizumab is currently underway and is one of the trials designed to evaluate this strategy.[41]

Chromophobe Renal Cell Carcinoma

Chromophobe RCC accounts for approximately 4% of all RCCs[9] and is often detected while still confined to the kidney, as less than 5% of cases are metastatic at the time of diagnosis.[26,27] The mechanisms underlying the genesis of this subtype of RCC are not well-understood. However, studies focusing on a familial form of chromophobe kidney cancer are beginning to provide some early insights that might help elucidate the molecular pathways driving this malignancy.

Birt-Hogg-Dubé (BHD) is an autosomal dominant hereditary cancer syndrome associated with bilateral, multifocal chromophobe RCC. Approximately, one-third of patients with BHD have this renal manifestation, with 5% demonstrating oncocytomas, and an additional 50% demonstrating hybrid chromophobe/oncocytic tumors.[42,43] The BHD gene, FLCN, located on the short arm of chromosome 17, was identified by genetic linkage analysis,[38,44] and is altered via insertion, deletion, or nonsense mutations in the germline of the vast majority of affected individuals.[45] The protein product of BHD, folliculin, functions as a tumor suppressor.[46] The function of folliculin and the consequences of folliculin loss in BHD are currently under study. Available data indicate that folliculin is a component of the cellular energy sensing system and may interact with cellular activated mitogen protein kinase (cAMPK) and mTOR pathways. Investigators at the National Cancer Institute have demonstrated mTOR upregulation in FLCN-/- tumors, with activation of both mTORC1 and mTORC2 pathways.[47] Additionally, the mTOR inhibitor rapamycin appears to ameliorate the renal phenotype and prolong survival in conditional FLCN-/- mice. These data suggest a role for mTOR inhibitors in the management of BHD-associated tumors. The relevance of the BHD and mTOR pathways in sporadic chromophobe RCC is an area of active investigation. It is hoped that these studies will help identify rational targets and help determine the utility of mTOR inhibitors in this patient population.

Upregulation of cellular proto-oncogenic receptor tyrosine kinase (c-KIT) has also been associated with chromophobe RCC;[48] however, its precise role in the genesis and progression of these tumors is unclear. C-KIT is a target that is amenable to pharmacologic inhibition, and several agents currently available, including imatinib, sunitinib, and sorafenib, have been shown to inhibit this molecule. Like papillary RCC, chromophobe tumors have been excluded from many of the initial targeted therapy trials. The available data are even more limited given that chromophobe RCC is less common and less likely to metastasize than papillary RCC, making attempts at subset analyses tenuous. Stadler and colleagues treated 20 subjects with chromophobe RCC as part of the Advanced RCC Sorafenib Expanded Access Program.[29] They saw an overall disease control rate of 90%, with 1 (5%) partial response and 17 (85%) subjects with stable disease for at least 8 weeks, while 2 (10%) subjects had disease progression. Chromophobe tumors were also included in the temsirolimus versus interferon alfa trial, but the published subgroup analysis by tumor histology only examined papillary tumors.[49] However, the OS and PFS were prolonged in the aggregate non-clear group treated with temsirolimus, providing evidence, albeit weak, for the use of temsirolimus over interferon alfa in advanced chromophobe RCC.

Collecting Duct Renal Cell Carcinoma

Collecting duct RCC is extremely rare, accounting for less than 1% of all RCCs[9] and is associated with a grave prognosis, with approximately one-third of patients having metastases at the time of diagnosis.[34] This malignancy is thought to arise from the collecting ducts of the renal medulla. Medullary carcinoma is an especially virulent type of the collecting duct RCC that is associated with sickle cell trait and is often seen in young African American patients.

Due to the rarity of this disease, there is scant

evidence to guide treatment recommendations, and no randomized clinical trials have been completed.[50] The strongest treatment evidence available comes from a phase II multi-center trial of 23 treatment-naive metastatic subjects who were given gemcitabine plus cisplatin or carboplatin, depending on renal function.[51] This regimen was selected based on the histologic similarities between the collecting duct RCC and transitional cell carcinoma of the urinary bladder. Oudard and associates found that 26% of subjects had a response to treatment per RECIST criteria (5 partial responses and 1 complete response) as measured by independent radiologic review; PFS was 7.1 months with an OS of 10.5 months.[51]

There is not enough data to comment on the role of TKIs or mTOR inhibitors in this type of RCC. Clearly more therapeutic options are needed for this disease.

Cytoreductive Nephrectomy, Neoadjuvant, and Adjuvant Therapy

Cytoreductive nephrectomy (CN) followed by systemic interferon was shown in two randomized trials to provide a statistically significant, albeit limited, improvement in survival (13.6 months for CN plus interferon versus 7.8 months for interferon alone when these two trials were analyzed in combination).[52-54] Based on these data, CN was adopted as the standard of care in the cytokine era. With the emergence of targeted therapies, the role of CN has not yet been directly re-evaluated with a randomized prospective study; however, the majority of subjects in the three major trials of sunitinib, sorafenib, and temsirolimus had undergone nephrectomy prior to receiving systemic therapy.[11-13]

The exact mechanism by which CN confers a survival advantage is still being elucidated, but potential explanations include removing bulky primary tumors which act as immunologic sinks for antibodies and tumor reactive lymphocytes, delaying disease progression, decreasing disease burden,[55] and reducing the amount of growth factors secreted by the primary tumor.[56] While most of these hypotheses were invoked to explain the utility of CN followed by cytokine therapy, some of these mechanisms may also be relevant in the era of targeted therapies designed to disrupt the proangiogenic pathways that are activated in RCC.

Prospective data on the use of CN in combination with targeted therapies in the metastatic clear cell RCC population are limited and this approach warrants further study. Phase III studies of sunitinib alone versus sunitinib with CN (CARMENA) and pre-surgical versus post-surgical sunitinib (EORTC) are currently ongoing in Europe.[57] In non-clear histologies, data from studies examining the role of CN are limited and largely based on retrospective subgroup analyses.[28,34,58]

Recently, Kutikov and colleagues published their series of 141 subjects, 98 of whom underwent CN and received systemic immunotherapy or targeted therapy between 1990 and 2008.[59] Of 132 subjects with an identifiable RCC histology, 7 (5.3%) had papillary and 2 (1.5%) had collecting duct RCC. Of these 9 subjects, 8 were able to receive systemic therapy following CN while 1 subject with the collecting duct RCC had rapid disease progression precluding systemic therapy. Across all histologies, rapid disease progression was the reason why 13 of 43 subjects (30%) could not receive systemic therapy after CN. The authors found that only poor baseline ECOG performance status predicted which subjects would not be able to receive post-CN systemic treatment, a conclusion that echoes those of prior studies.[60]

Some authors consider non-clear histology to be a relative contraindication to CN given the scant data available to support a survival advantage, the known morbidity, and possible mortality that is associated with the procedure.[57] However, given the limited systemic options available, aggressive surgical resection in appropriately selected candidates seems to offer the patient with advanced or metastatic non-clear RCC the best chance for prolonged survival currently available. Additional trials are needed to address how to identify the optimal candidate for CN, which systemic targeted therapy agent or agents to use, and in what order to employ them.

Neoadjuvant systemic therapy has been shown to benefit patients with advanced bladder, metastatic germ cell, and metastatic colon cancer. No trials directly address the use of neoadjuvant systemic targeted therapy for non-clear RCC, but several case series have been published and several centers, such as M.D. Anderson Cancer Center, University of North Carolina at Chapel Hill, and the Cleveland Clinic have active protocols addressing this issue; however, none are exclusively focused on non-clear histologies.[61] The goals of neoadjuvant therapy are to downstage the primary tumor in order to make extirpative surgery feasible or technically less challenging and to eradicate micrometastatic disease, as distant failure portends a poor prognosis.[55,62] A significant portion of patients undergoing aggressive surgical resection fails to receive systemic therapy because of rapid disease progression.One treatment strategy described by Margulis and Wood at M.D. Anderson Cancer Center is to treat surgically unresectable patients with sunitinib for four weeks followed by restaging.[63] Patients with a favorable response can proceed to extirpative surgery while those who fail to respond or progress are treated with a different systemic agent. The goal of this schema is to identify those patients who are likely to progress rapidly and therefore never receive adjuvant therapy after CN, and treat them systemically while avoiding the morbidity of major surgery. This is an intriguing study design and should be replicated in the setting of non-clear histology, particularly once active systemic agents become available.

The use of cytokine therapy in the adjuvant setting to reduce the risk of distant failure following local treatment with curative intent was not found to be beneficial in patients with clear cell RCC.[64-66] Adjuvant targeted therapies are now being evaluated with trials in the United States, Europe, and Asia.[8] For example, the Eastern Cooperative Group sponsored ASSURE (Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma) trial is open to all histologies except collecting duct or medullary carcinoma; enrollment is ongoing, but no results have been reported. Southwest Oncology Group's EVEREST (Everolimus in Treating Patients with Kidney Cancer who have Undergone Surgery) is open to all histologies except the collecting duct or medullary RCC and compares everolimus to placebo in the adjuvant setting. Similarly, the industry-sponsored S-TRAC (Sunitinib Treatment of Renal Adjuvant Cancer) is also open to all RCC subtypes except the collecting duct and is accruing subjects. The United Kingdom's Medical Research Council-sponsored SORCE (Sorafenib in Treating Patients at Risk of Relapse after Undergoing Surgery to Remove Kidney Cancer) is open to all histologies, but as expected in an adjuvant trial, nephrectomy is the only prior RCC treatment allowed.

FUTURE RESEARCH

Despite recent advances, there remains a paucity of effective systemic options directly applicable to advanced and metastatic non-clear cell RCC. Histology-specific and mechanism-based studies addressing virtually all aspects of papillary, chromophobe, and the collecting duct RCC are essential for continued progress in our attempts to determine optimal management of these patients.

The identification of several familial forms of renal cancer has greatly enhanced our ability to study and understand the genetic alterations and biochemical pathways unique to distinct subtypes of RCC. As with clear cell RCC, better molecular characterization will likely enable development of rational targeted strategies against other subtypes of familial kidney cancer as well as their sporadic counterparts. Due to the rarity of these conditions, multi-center cooperative trials have the highest likelihood of accruing enough subjects to adequately power prospective studies.

Several agents currently available demonstrate modest activity in patients with non-clear cell RCC. Trials investigating combinations of one or more of these agents, either administered in sequence or given concomitantly, may improve outcomes compared to monotherapy by allowing targeting of multiple pathways of tumorigenesis simultaneously. Neoadjuvant targeted therapy with or without CN is likely to become increasingly relevant in the management of selected patients with advanced clear cell RCC. Its role in the non-clear patient population

must be elucidated further. Risk factors other than performance status must be identified to properly stratify patients given the morbidity of CN and the high percentage of patients who rapidly progress despite systemic therapy. Histology-specific circulating tumor markers are quite promising in this regard[61,67] and may help identify who should receive systemic treatment immediately instead of CN, as well as serve as non-radiographic (non-RECIST) surrogates or predictors of tumor response.[8] Similarly, the optimal duration of and timing between neoadjuvant treatment and CN need further definition; however, reports have not described significant problems with wound healing or other increased morbidity thus far.[62,63,68]

The impact of targeted therapies on patient's quality of life must also be examined along with the more traditional oncologic endpoints of adverse events, disease progression, and survival.[69] Targeted therapies offer tremendous therapeutic opportunities to patients, but also come with unique and often unavoidable side effects.[70] A number of validated, cancer-specific, and kidney cancer-specific instruments exist, but there are neither histology-specific nor widely accepted standard quality of life surveys for RCC at this time.[71] Quality of life endpoints should be included in all prospective targeted therapy studies and considered as an essential component for multi-center and cooperative group trials in order to ensure that the goal of alleviating suffering is advanced along with the goals of prolonging survival and identifying cures for patients with non-clear RCC.

CONCLUSION

Targeted therapies have greatly expanded the treatment options available to patients with advanced and metastatic non-clear cell RCC. However, much work is needed in order to determine the optimal agent(s) against each histologic subtype.

Patients presenting with advanced non-clear pathology should undergo a thorough metastatic evaluation and, if appropriate, surgical evaluation to determine if nephrectomy, lymphadenectomy, and/or metastectomy are warranted. Aggressive surgical extirpation is often recommended at the National Cancer Institute given the poor survival associated with these entities and the limited evidence available to drive the selection of systemic therapy.

All patients should be encouraged to consider participating in clinical trials and referred to appropriate medical centers. At the present time, the literature offers limited support for the use of VEGF and mTOR inhibitors to treat patients with advanced or metastatic non-clear cell RCC. The results of prospective trials examining treatments for papillary, chromophobe, and the collecting duct RCC are eagerly awaited.

CONFLICT OF INTEREST

None declared.

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