Therapeutic Options for Variant Renal Cancer: A True Orphan Disease

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ABSTRACT

Variant or nonclear cell renal cell cancer is a rare disease constituting only ~5% to 8% of the metastatic renal cell cancer population. Pathological criteria for the three main variant subtypes, papillary, chromophobe, and collecting duct, have been specified. Nonetheless, there may be subtypes within these variants, many poorly differentiated tumors cannot be reliably classified, and expertise in recognizing specific subtypes is not widespread. Expression analysis and other molecular techniques are beginning to clarify and standardize the pathological classification scheme. Because these classifications are relatively new and the number of patients with any one subtype is limited, little is known about appropriate therapies for patients with metastatic disease. Retrospective series strongly suggest that immunotherapy is not effective in any nonclear cell subtype. Case reports suggest that cytotoxic chemotherapy used for transitional cell cancers may be helpful in patients with collecting duct cancers. A central registry of patients with variant renal cell cancer should be created in which response to various therapies is recorded. Such a registry could provide support for a more formal multi-institutional study investigating a specific drug or regimen.

INTRODUCTION

Until recently, all adult renal epithelial malignancies were considered one disease labeled renal cell carcinoma. During the last 10 years, however, renal cell carcinoma has been increasingly recognized as several different subtypes that have distinct biological attributes, pathological characteristics, and likely oncogenesis (1, 2). As such, renal cell carcinoma is best thought of as several separate diseases for which unique and specific therapeutics must be developed. To begin to develop specific regimens for each subtype, especially the less common ones, a brief review of their biology and the effectiveness of available therapy is in order.

Renal cell carcinoma can be divided into classic clear cell carcinoma, papillary carcinoma, chromophobe carcinoma, and collecting duct carcinoma (3). Despite consensus on broad categories of nonclear cell carcinoma of the kidney, additional subsets for which the relationship is somewhat unclear continue to be described. Papillary cancers have, for example, been subdivided into type 1 and type 2 (4), and some controversy remains regarding whether medullary cancers, which have been described almost exclusively in patients with sickle cell disease or trait, are a variant of collecting duct carcinoma (5). In addition, a number of poorly differentiated tumors exist, often classified as sarcomatoid, in which unique pathological characteristics cannot be recognized. Unfortunately, expertise in recognizing even the standard subtypes varies dramatically. Finally, mixed histologies are not uncommon, and the biological significance of such findings is unclear. More importantly, much of the therapeutic literature for renal cell carcinoma either does not subclassify patients by histologic characteristics or uses histologic classifications that are no longer considered standard.

GENETICS AND BIOLOGY

Classic molecular genetics, cytogenetics, and expression profiling have clarified some of the relationships among the various histologic subtypes. The proposed two papillary subtypes are indeed closely related genetically (4). Similarly, chromophobe tumors are molecularly closely related to benign oncocytes, whereas collecting duct carcinomas and medullary carcinomas are likely more closely related to transitional cell carcinomas (6, 7). Additional expression profiling studies and the use of specific molecular probes and immunohistochemical markers will likely serve to further standardize and define the various renal cell carcinoma subtypes.

Despite the power of molecular profiling, from a therapeutic standpoint it is most important to identify those molecular alterations that are critical to the malignant phenotype of a particular tumor. To this end, the identification of the initiating genetic alterations, similar to the bcr-abl translocation in chronic myelogenous leukemia, is critical. The study of familial renal cell carcinoma has provided several clues to potential genes critical for the renal cell carcinoma phenotype. In the classic clear cell carcinomas and as described elsewhere (8), study of the von Hippel-Lindau (VHL) syndrome has proved important. The VHL gene product, which is inactivated in the germ line of VHL syndrome patients and in the clear cell renal cell carcinoma tumor cells (9, 10), targets the hypoxia-inducible factor (HIF) transcription factor for ubiquitin-mediated destruction in a normoxic environment (11–13). In the absence of a functional VHL gene product, HIF remains active and mediates the transcription of, among other factors, vascular endothelial growth factor (VEGF), platelet-derived growth factor, and carbonic anhydrase IX (12, 13). These genes contribute to the known hypervascularity of these tumors and may explain the recently described activity of the anti-VEGF antibody bevacizumab, as well as the VEGF receptor and platelet-derived growth factor.

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receptor tyrosine kinase inhibitors BAY 43–9006 and SU11248 in this disease (14–16).

Familial nonclear cell renal cell carcinomas have also been described, and several germ line-mutated genes putatively responsible for the observed phenotypes have been identified (2). For example, familial type I papillary cancers have been characterized by MET oncogene mutations that lead to activation of this growth factor receptor tyrosine kinase (17). As a result, the pathway is activated even in the absence of its natural ligand, heptic growth factor (also known as scatter factor; ref. 18). Familial type II papillary cancers have been associated with cutaneous and uterine leiomyomas and mutations in fumarate hydratase (19–21). The mechanism behind oncogenesis after mutation of this metabolic enzyme is currently not known. Finally, familial Birt-Hogg-Dubé (BHD) syndrome has been associated with multiple renal tumors (usually of the chromophobe subtype) in addition to skin fibrofolliculomas and pulmonary cysts (22). The responsible tumor suppressor gene, the BHD gene, has been identified recently, and some of the mutations in the familial kindreds have been described (23, 24).

However, in all of these cases, and unlike the role of VHL in clear cell cancers, the role of these genes in sporadic forms of each nonclear cell histologic subtype is less clear. For example, MET mutations are very rare in patients with sporadic papillary cancer (25). Although immunohistochemical-based expression of c-MET has been described in the sporadic forms of papillary renal cell carcinoma, the physiologic relevance of this finding remains unclear (26). The BHD gene is occasionally inactivated in spontaneous renal cell carcinomas of various subtypes, but once again whether this is important to the malignant phenotype remains unknown (27). Perhaps more important is the fact that the role of other members of genetic and metabolic pathways inactivated in the familial nonclear cell cancers have not been investigated. Therefore, unlike the case in clear cell renal cell carcinoma in which VEGF receptor and platelet-derived growth factor receptor can be therapeutically targeted, putative therapeutic targets in nonclear cell renal cell carcinoma remain to be identified.

INCIDENCE AND NATURAL HISTORY

The incidence of nonclear cell carcinoma of the kidney has been reported as ~20% to 30%, with papillary cancers constituting 10% to 15%, chromophobes constituting 5%, and collecting duct constituting ~1% of cases (1, 28). These numbers, however, reflect data from surgical series of primary nephrectomies. Because primary nonclear cell carcinomas tend to have a better prognosis than clear cell carcinomas, the percentage of metastatic nonclear cell carcinomas is much lower (28). Recent reviews from Memorial Sloan-Kettering Cancer Center (New York, NY; ref. 29), the Cytokine Working Group, (30), and the University of Chicago (Chicago, IL; ref. 31) suggest that only 5% to 8% of patients treated in clinical trials have nonclear cell histologic characteristics.

The Memorial Sloan-Kettering Cancer Center investigators have also reported on the natural history of metastatic nonclear cell cancers (28). In contrast to the localized setting, metastatic papillary cancers have a relatively poor prognosis, with a median survival of 5.5 months. Patients with metastatic collecting duct cancer have a slightly better median survival at 11 months, whereas patients with metastatic chromophobe cancer have a rather long median survival of 29 months.

TREATMENT

The data for response of nonclear cell renal cell carcinoma to available therapies used in clear cell carcinoma are rather sketchy. This is not only because of the rarity of these variants in the metastatic setting, but also because, as noted, older studies have not typically reported on response by subtype. More recently, the Cytokine Working Group has reported that only 1 of 17 patients with nonclear cell tumors responded to high-dose interleukin 2, (30) and in the Memorial Sloan-Kettering Cancer Center series, only 1 of 37 responded to interferon-based therapy (29). None of the 5 nonclear cell carcinomas responded to gemcitabine and 5-fluorouracil in the University of Chicago series (31). There are a number of case reports describing responses of collecting duct carcinoma to gemcitabine or taxane-based therapies similar to those used in transitional cell carcinoma (32, 33). This is consistent with expression data that suggest that these tumors are closely related to transitional cell cancers (5, 6). Although these data strongly suggest that immunotherapy is not particularly effective for nonclear cell renal cell carcinoma, it is clear that the current data are inadequate for assessing the value of almost any other drug in these diseases.

There are a number of strategies that can be envisioned to assess and identify new agents for patients with nonclear cell renal cell carcinoma. Patients could be enrolled in general renal cell carcinoma Phase II trials, and subgroup analyses could then be attempted. However, only one or two variant cancers are likely to be enrolled in any typically sized Phase II trial, and most modern Phase III trials are appropriately excluding patients with nonclear cell histologic characteristics. Cooperative group studies could potentially perform trials specifically for such patients. However, there are ~12,000 patients with metastatic kidney cancer annually, and as noted only ~5% have a variant histologic subtype. There are, thus, <600 patients who develop any one of these diseases on an annual basis in the United States. With the current rate of enrollment into clinical trials in the adult oncology community, even a cooperative group trial would likely take several years to accrue. This raises the issue of how to wisely choose agents for additional development.

Choosing appropriate agents will clearly depend on improvements in understanding the biology of nonclear cell carcinomas. Expression profiling, cell lines, and animal models can all provide potential predictive information. It is important to recognize, however, that activation or overexpression of a particular pathway is not enough to make that pathway a good therapeutic target. The molecular abnormality has to be necessary for malignant growth.

In the meantime, decisions will have to be based on clinical observations. To this end, a clinical registry of nonclear cell carcinomas may be helpful. Major centers all evaluate two to eight patients with nonclear cell renal cell carcinoma annually and typically treat them with a variety of regimens, including off-protocol therapy, Phase I clinical trials, and occasionally Phase II clinical trials with broad eligibility. If a registry reveals
that several patients with a specific renal cell carcinoma subtype have responded to a particular class of agents, this might be sufficient to justify a larger cooperative group clinical trial. The value of such a registry can be illustrated by anecdotal observation of responses to Gleevec in gastrointestinal stromal tumors, which led to identification of the pathognomonic c-kit inactivation in these tumors and a collaborative group of investigators dedicated to performing therapeutic studies (34).

CONCLUSIONS

Nonclear cell or variant metastatic renal cell carcinomas are unique diseases that will require unique therapeutic approaches. The recognition of these subtypes by general pathologists is improving, and molecular diagnostics are likely to additionally improve the diagnostic accuracy. Nevertheless, the rarity of these diseases in the metastatic setting means that they are truly orphan diseases for which it is extremely difficult to conduct clinical trials. Therefore, a clinical registry should be created in which response to various off-protocol and early phase clinical trials are recorded. In addition to ongoing work on the biological pathways important in these diseases, such a registry may provide clues to which classes of agents may be therapeutically effective.

OPEN DISCUSSION

Dr. Michael B. Atkins: Do you know of any patients with nonclear cell histology who have had a response to some of the other targeted agents?

Dr. Daniel J. George: We had two patients with chromophobe tumors who had a minor response on PTK787. I think that is all you are going to find in these kinds of studies. These tumors are not that dissimilar in terms of their biology, although genetically they are. I think there is a reason to try some of these VEGF targeted strategies in patients with nonclear cell histology.

Dr. Atkins: But the reason is the same reason you would try it in colon cancer or in any other cancer.

Dr. George: Yes, that’s right. If I have a patient with a chromophobe tumor, I would be willing to enroll him on a Phase I study with a VEGF inhibitor.

Dr. William G. Kaelin, Jr.: Would it be fair to make the argument that there is as much heterogeneity with what we call clear cell carcinoma as with other types of cancer?

Dr. Walter M. Stadler: There is a huge difference between clear cell and other cell types, but within the clear cell, there are different subgroups. We don’t know why, but that is the reason for the difference in response within that larger clear cell group.

Dr. Kaelin: Do we decide that from now on we are going to treat the VHL mutant clear cell population differently as opposed to treating all clear cell the same or do we want to allow for empiricism and include everybody?

Dr. Bin Tean Teh: For this case, that is, the so-called nonclear cell, it is very important to make sure that the diagnosis is correct.

Dr. Stadler: We need better diagnostics, but I think we are fairly close to being very accurate in terms of how we diagnose these different subtypes. It still leaves us with the question of how we develop therapies for some of these subtypes that are extremely rare. We have too few patients, too many drugs, and not necessarily a good rationale.

Dr. Robert A. Figlin: Some of my most difficult decisions these days are deciding what to do with the patients with pure papillary tumors. There are a variety of things out there, but there is not a lot of information that suggests that we have any knowledgeable approach to this patient population. Are we talking about papillary tumors or are we talking about tumors that have wild-type VHL?

Dr. Stadler: We are talking about the nonclassic clear cells, those with wild-type VHL.

Dr. Atkins: So, this could be up to 40% of the patients.

Dr. Figlin: Correct. I’m just wondering whether we need to start thinking about approaching kidney cancer as diseases with either mutated or nonmutated VHL.

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Clinical Cancer Research

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*Clin Cancer Res* 2004;10:6393S-6396S.

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