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Renal carcinoma pharmacogenomics and predictors of response: Steps toward treatment individualization

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Abstract

Molecular knowledge has deeply affected the treatment and outcome of kidney cancer in recent years, and several therapeutic options have become available. However, there are no validated biomarkers to select the best drug for each patient. Already published studies and ongoing investigations could change this scenario in the near future. Regarding antiangiogenic drugs, several works on single nucleotide polymorphisms have achieved promising results, with some SNPs predicting resistance to sunitinib and pazopanib being validated. If more evidence is gained, it could prompt prospective studies exploring a molecularly driven selection of treatment. Another relevant line of investigation for antiangiogenic drugs is the cytokines and antiangiogenic factors. Different studies have found that cytokines and antiangiogenic factors are able to predict the outcome of patients treated with sunitinib, pazopanib, or sorafenib. Issues regarding the thresholds of normality and the best time for assessment are pending, but the communicated results are encouraging. Less evidence is available for mammalian target of rapamycin inhibitors but recent data support a key role of the phosphoinositide 3-kinase/Akt pathway in clear cell renal cell carcinoma and points toward poor response to angiogenic drugs when the pathway is activated. Whether modern phosphoinositide 3-kinase inhibitors could be the best option for these patients is a question that should be addressed. Additionally, a new class of immunomodulators, like anti–programmed death 1 drugs, has demonstrated to achieve long-lasting stabilizations even in some patients with no radiological response or early progression. This is a singular situation where the identification of reliable predictors of efficacy will be key in the development of these drugs in renal cell carcinoma. Finally, germline mutations of the *c-Met* gene have been proposed as the first predictor of response to targeted therapies in papillary renal cell carcinoma. As a conclusion, translational research will be a cornerstone to move a next step forward in kidney cancer.

Keywords: Kidney cancer; Clear cell renal carcinoma; Targeted therapies; Predictive biomarkers; Antiangiogenics; mTOR inhibitors

Introduction

Major successes achieved in recent years in clear cell renal cell carcinoma (ccRCC) treatment have been based on the molecular knowledge of the disease. This knowledge has led to the approval of 8 agents in this setting (1 antibody against the vascular endothelial growth factor [VEGF]: bevacizumab; 4 inhibitors of its receptors [VEGFR]: sorafenib, sunitinib, pazopanib, and axitinib; 2 inhibitors of the mammalian target of rapamycin [mTOR]: temsirolimus and everolimus; and 1 recombinant form of an endogenous cytokine: interleukin-2 [IL-2]). However, no advances to match the best therapeutic option to each patient have been made. Thus, after an improvement in outcomes with introduction of the initial targeted agents, outcomes have since plateaued and the huge effort of including thousands of patients in clinical trials assessing different combinations of drugs or sequential strategies of treatment has failed to affect overall survival (OS) of RCC.

A "new generation" of studies focusing on molecularly defined populations of patients could be the way to take advantage of the currently available therapeutic arsenal. This review focuses on the so far published approaches toward the individualization of RCC treatment, and gives

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some clues of expected results and needs for the future. The next sections summarize potential predictive biomarkers proposed for the different RCC drugs.

Classical immunotherapy

Interferon (IFN) and IL-2 were largely used in kidney cancer before the development of targeted therapies [1]. Even today, IFN, combined with bevacizumab, and high-dose IL-2, for selected cases, are accepted options in the first-line setting of ccRCC [2]. Concerning markers of response, in 2005 Atkins et al. [3] communicated the results of a nested case-control study of 66 patients with metastatic ccRCC who had received IL-2 within different clinical trials. They described an association between CAIX expression, assessed by immunohistochemistry, and response to IL-2 ($P = 0.04$). Unfortunately, a prospective validation study (the SELECT study) failed to confirm those results [4]. Thus, currently there are no predictive markers available for cytokine immunotherapy.

Modern immunotherapy

Promising results have been recently communicated with the new immunomodulator, nivolumab (BMS-936558), a monoclonal antibody against programmed death 1 (PD-1) [5]. A response rate of 27% in 33 patients with metastatic RCC was achieved. None of the tumors lacking PD1 expression did respond, suggesting PD1 as a biomarker to identify resistant tumors. Confirmatory studies to determine the activity of the drug in RCC and the reliability of PD1 expression as a predictive marker are ongoing. The identification of accurate biomarkers will be key to further develop this class of drugs, because they may not produce immediate radiological responses, and "pseudoprogressions" (initial tumor growth in patients that finally responded) have been described in some cases [6].

Antiangiogenics

Antiangiogenic drugs have become the cornerstone of kidney cancer treatment. Though they all share the VEGF pathway as their main target, relevant differences in the mechanism of action and the spectrum of tyrosine kinases inhibited could make a difference in some populations of patients.

Sunitinib

Von Hippel-Lindau (VHL) gene status

VHL inactivation plays a key role in ccRCC and provides the rationale for the development of antiangiogenic drugs to treat this tumor [7]. In 2008, a retrospective study assessed the value of such alteration as predictor of response in patients with ccRCC treated with any of the 4 different drugs (sorafenib, sunitinib, bevacizumab, and axitinib) in 2 institutions in the United States as continuation of a prior work by Rini et al. [8,9]. Up to 123 patients of 183 cases could finally be analyzed for both *VHL* mutations and gene methylation. *VHL* mutations were found in 60 (49%) and methylation in 12 tumors (10%). A nonsignificant trend toward a better response rate (41% vs. 31%) was found in tumors with VHL inactivation. Such difference became significant in a post hoc analysis when only loss of function mutations were considered. More recently, Garcia-Donas et al. [10] also studied *VHL* mutations and loss of expression in a prospective cohort of 101 patients treated with first-line sunitinib (SUT-REN 07 study). Of the 31 patients that could be analyzed, 64% presented *VHL* inactivation, and no association with outcome was observed. Importantly, it must be noted that the average number of cases with *VHL* inactivation, around 60% in both communications, is far from the 91% reported by some authors [11]. Thus, a more accurate determination of the VHL status and larger sample sizes would be mandatory to reach a reliable conclusion. VHL status is not clinically useful at present.

Polymorphisms

Single nucleotide polymorphisms (SNPs) have been a major area of interest for researchers in ccRCC (Table 1). As normal endothelial cells and circulating VEGF are the true target of antiangiogenic drugs, the genetic background of the patient could play a critical role determining not only tolerability but also efficacy.

Focusing on toxicity, van Erp et al. [12] assessed, in 2009, 31 polymorphisms in 219 patients diagnosed with renal or gastrointestinal stromal tumors treated with sunitinib. The strongest associations in multivariable analysis were found for the following: leukopenia, *FLT3* rs1933437 (T227M), and *CYP1A1* rs1048943 (I462V); mucosal inflammation and *CYP1A1* rs1048943; any toxicity >grade 2; and *VEGFR2* rs2305948 (V297I). A later publication by the same group suggested a protective role for the *FLT3* rs1933437 polymorphism in bone marrow toxicities [13]. In 2011, the SUT-REN 07 study communicated that the SNP *CYP3A5*1* (rs776746) was associated with an increased risk of sunitinib dose reductions owing to toxicity (HR = 3.7, 95% CI = 1.7–8.4, $P = 0.001$) [14]. This association was significant after correction for multiple testing. In the same publication, some other SNPs were also associated with hypertension risk: *VEGFR2* rs1870377 (Q472H), *ABCB1* rs1128503 (G412G), and *VEGFA* rs699947 (−2578A > C). More recently Kim et al. [15] evaluated 63 patients with mRCC treated with sunitinib and found an association for the *VEGF* SNP rs2010963 (−634G > C) and higher risk of hypertension.

Concerning efficacy, van der Veldt et al. studied 136 patients with ccRCC, which included those reported formerly by van Erp et al [16,13]. The SNPs *CYP3A5* rs776746, 2 *NR1I3* and *ABCB1* haplotypes, and *VEGFR2* rs1870377 presented the strongest association with survival. García-Donas et al. in the SUT-REN 07 study, found a highly significant association between 2 *VEGFR3* polymorphisms, rs307826 (T494A) and rs307821 (R1324L),