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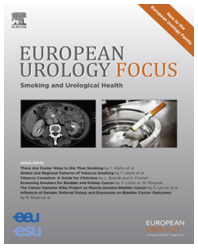

Kidney Cancer

Correlation Between Molecular Subclassifications of Clear Cell Renal Cell Carcinoma and Targeted Therapy Response

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Abstract

Background: Vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR)–directed therapies are the standard of care in metastatic clear cell renal cell carcinoma (mccRCC) but are not used based on molecular subclassifications of ccRCC.
Objective: To determine if an association exists between genomic alterations (GAs) detected by comprehensive genomic profiling (CGP) in the course of clinical care and the response to anti-VEGF receptor (VEGFR) and anti-MTOR pathway targeted therapies in a cohort of patients with treated mccRCC.
Design, setting, and participants: CGP, using a Clinical Laboratory Improvement Amendments–certified platform, was performed on 31 formalin-fixed, paraffin-embedded tissue specimens (84% from cytoreductive nephrectomies) obtained from patients with metastatic renal cell carcinoma who had received VEGFR and/or mTOR inhibitors. Duration of treatment (DOT) and extent and duration of clinical response were obtained from review of medical records.
Outcome measurements and statistical analysis: All classes of GAs—base substitutions, short insertions, deletions, gene fusions, rearrangements, and copy number—were assessed via hybrid capture-based CGP. Descriptive statistics were used to determine the frequency of GAs in groups segregated by the DOT with VEGF-directed agents.
Results and limitations: The most common GAs detected in this series were in *VHL* (70%), *PBRM1* (48%), *SETD2* (32%), *TSC1* (29%), *MLL* (19%), *TERT* (16%), *ARID1B* (16%), and *KDM5C* (16%). Across 61 administrations of VEGF-directed therapy in 27 patients, exceptional responses (DOT >21 mo) were more frequent among patients with GAs in *KDM5C*, *PBRM1*, and *VHL*. Conversely, these patients also featured a lower frequency of GA associated with response to mTOR-directed therapy, such as *TSC1*.
Conclusions: Molecular subclassifications may affect response to VEGF-directed therapy. The predictive and prognostic nature of these molecular subclassifications in the metastatic setting should be explored in an extended series.
Patient summary: Comprehensive genomic profiling in the course of clinical care in the community oncology setting can delineate subgroups of patients with advanced kidney cancer who stand to benefit more from specific molecular-targeted agents.

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1. Introduction

The treatment of metastatic renal cell carcinoma (mRCC) has evolved drastically over the past decade with the introduction of seven US Food and Drug Administration–approved targeted therapies[1]. These therapies coalesce into two groups, as defined by likely mechanism of action: (1) inhibitors of mammalian target of rapamycin (mTOR) and (2) inhibitors of the vascular endothelial growth factor receptor (VEGFR) and its ligand. An improvement in survival has been clearly documented in the era of targeted therapies as compared with the cytokine era: Median survival has improved from an estimated 12 mo with treatments such as interferon-α to nearly 3 yr in more recent prospective studies of VEGF- and mTOR-directed agents [2–4]. Despite these improvements, an apparent paradox relative to the practice of modern oncology exists: Targeted treatments are applied without assessing the genomic profile of the tumor in individual patients, in contrast to the paradigm of *ALK*-rearranged non–small cell lung carcinomas and matched use of approved ALK tyrosine kinase inhibitors such as crizotinib. Multiple efforts have been made, with limited success, to characterize predictive biomarkers for mTOR- and VEGF-directed therapy. Expression of VEGF, mTOR, and other pathway members has also failed to consistently predict response. In contrast to these findings, recent retrospective correlative efforts accompanying the RECORD-3 trial (comparing sunitinib and everolimus in the front-line setting) identified several predictive recurrent genomic alterations (GAs) in clear cell renal cell carcinoma (ccRCC), using retrospective, targeted next-generation sequencing (NGS) [5–8].

We assessed a cohort of patients who were receiving targeted therapies for mccRCC in two academic practices but who were not enrolled in a clinical trial. To identify molecular subclassifications of ccRCC, comprehensive genetic profiling (CGP) was performed for patients in this series during the course of clinical care, using an assay offered by a central laboratory (Foundation Medicine, Inc, Cambridge, MA, USA). We highlight GAs that may be associated with enhanced responses to targeted therapy in ccRCC.

2. Materials and methods

2.1. Patient selection

Patients included in the current series had histologically confirmed RCC and had radiographic evidence of metastatic disease. Patients had received VEGF-directed and/or mTOR-directed therapies as a part of routine clinical care at one of two institutions (Mayo Clinic or City of Hope) and complete information was available regarding both the date of initiation and discontinuation of these treatments. Episodes of treatment were excluded if VEGF- or mTOR-directed therapy was ongoing or if therapy was discontinued because of toxicity, as opposed to clinical or radiographic progression. Notably, the patients reported in this study represent the totality of all patients meeting these inclusion/exclusion criteria at the participating institutions.

After approval from the Mayo Clinic and City of Hope institutional review boards, demographic characteristics, including age, race, and sex, were collected for all patients in the current cohort. Furthermore, the following variables were collected to ascertain International Metastatic Renal Cell Database Consortium (IMDC) risk score: (1) Karnofsky performance status, (2) time from mRCC diagnosis to treatment, (3) presence or absence of anemia, (4) presence or absence of thrombocytopenia, (5) presence or absence of neutrophilia, and (6) presence or absence of hypercalcemia. An IMDC risk score was subsequently assigned to each patient in the series based on previously published criteria [9]. Pathologic features, including size and extent of primary tumor (summarized as the T stage) and Fuhrman grade, were also collected.

2.2. Comprehensive genomic profiling

Formalin-fixed, paraffin-embedded (FFPE) tissue specimens included in the current series were analyzed using the methods described, which were previously published elsewhere in greater detail [10]. All specimens included in the current series were obtained for the purpose of aiding routine clinical care. Briefly, FFPE slides or blocks were obtained. Genitourinary pathologists selected the appropriate blocks that were composed predominantly of tumor cells that appeared histologically viable and had >60% tumor nuclei and <20% necrosis of sample volume. The criteria were based on the Cancer Genome Atlas (TCGA) tissue requirements. DNA was extracted, and CGP based on targeted NGS of established cancer-related genes was performed on hybridization-captured, adaptor ligation-based libraries in a Clinical Laboratory Improvement Amendments-certified laboratory (Foundation Medicine, Inc). All exons for 315 cancer genes were analyzed, with introns of 31 genes frequently rearranged in cancer. Specimens were sequenced to a median depth of >650×. Base substitutions, short insertions, deletions, gene fusions, rearrangements, and copy number changes were assessed [11,12]. Bayesian algorithms were used to detect substitutions and local assembly algorithms to detect insertions/deletions, and a comparison to normal control samples was used to detect copy number alterations.

2.3. Correlation of clinical outcome and genomic data

Given the challenges in retrospectively defining progression, the primary objective of the current study was to correlate duration of treatment (DOT) with genomic data in the current study. DOT was defined as the time elapsed between initiation of targeted therapy and the date of discontinuation of treatment. Patients were segregated into groups based on DOT, with cut-offs at 3, 6, 9, 12, 15, 18, and 21 mo; cut-offs beyond this were not used, given the rarity of patients with such extensive time on treatment. Descriptive techniques were used to (1) generate a heat map defining the frequency of mutations across cohorts segregated by DOT and (2) compare cumulative mutational frequencies in the overall cohort to previously published experiences (ie, the TCGA data set) [5].

3. Results

3.1. Patient characteristics

In total, 31 patients with metastatic ccRCC were identified as meeting the specified eligibility criteria (Table 1). Among these, 27 patients (87%) had received VEGF-directed therapy and a smaller proportion of patients (39%) had received mTOR-directed therapy. Within this subset, the majority of patients were male (81%) and white (85%), with a median age of 61 years. By IMDC risk group, the majority of patients (74%) were characterized as intermediate risk. Patients had been exposed to a wide range of therapies previously, with 59% of patients having received three or more prior treatments. With respect to standard pathologic assessment, a wide range of patients was represented based on Fuhrman grade and T stage.

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