Original Study

Genomic Characterization of Renal Medullary Carcinoma and Treatment Outcomes

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Abstract

Renal medullary carcinoma (RMC) is a rare kidney cancer with poor outcomes. We analyzed treatment outcomes in patients with RMC and performed targeted sequencing of tumors to identify unique molecular features. Although responses to platinum-based therapy were found, these were short-lived. There was uniform loss of SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily B, Member 1 (SMARCB1) through translocations and deletions, and further research should go into targeting this pathway.

Background: Renal medullary carcinoma (RMC) is a rare and aggressive type of kidney cancer that primarily affects young adults with sickle cell trait; outcomes are poor despite treatment. Identifying molecular features of this tumor could provide biologic rationale for novel targeted therapies. The objective was to report on clinical outcomes with systemic therapy and characterize molecular features. **Patients and Methods:** This was a retrospective analysis on 36 patients given a pathologic diagnosis of RMC at one institution from 1995 to 2015. Tumors were analyzed for expression of SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily B, Member 1 (SMARCB1) through immunohistochemistry and for genomic alterations with fluorescence in situ hybridization for SMARCB1, and targeted next-generation sequencing. Time from initiation of therapy to progression of disease and overall survival were calculated using the Kaplan–Meier method. **Results:** The median age in the cohort was 28 (range, 12-72) years, and all patients tested had sickle cell trait. Overall survival was 5.8 months (95% confidence interval [CI], 4.1-10.9) and for 12 patients who received platinum-based therapy, median progression-free survival was 2.5 months (95% CI, 1.2-not reached). A total of 10 available tumors underwent analysis with fluorescence in situ hybridization for SMARCB1; this revealed loss of heterozygosity with concurrent translocation in 8, and biallelic loss in 2. Next-generation targeted sequencing showed no recurring mutations. **Conclusions:** Outcome was generally poor in this cohort of patients with RMC. Uniform loss of SMARCB1 is a key molecular feature in this tumor and mechanism of loss appears to be mostly through translocations and deletions.

Clinical Genitourinary Cancer, Vol. ■, No. ■, 1-7
Keywords: Chemotherapy, Genomics, Kidney cancer, Retrospective analysis, SMARCB1

Introduction

Renal medullary carcinoma (RMC) is a rare and aggressive type of kidney cancer that primarily affects young adults with sickle cell trait. It was first described in 1995, when Davis et al reported on a series of cases of aggressive kidney cancer whose histology predicted presence of red blood cell sickling. Since then, other series have confirmed that most affected patients have either sickle cell trait, or rarely, sickle cell disease, with a median age of diagnosis ranging between 15 and 26

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Submitted: Mar 10, 2017; Revised: Apr 13, 2017; Accepted: Apr 14, 2017

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1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2017.04.012

years.[1-3] Most patients present with advanced disease and, despite therapy, overall survival (OS) is usually < 1 year.

There is no defined standard treatment for this rare entity. Most patients receive platinum-based therapy on the basis of extrapolation from therapies used in other distal nephron tumors, however, there have been no prospective studies or large retrospective series to validate this approach. Small retrospective series have reported that only a small number of patients respond to chemotherapy.[4] Targeted therapy with vascular endothelial growth factor (VEGF) inhibitors or mammalian target of rapamycin (mTOR) inhibitors have also been used with disappointing results.[5]

Because of the aggressive nature and poor outcomes of this disease, there is great need to identify novel molecular therapeutic targets. Several studies have reported loss of expression of SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily B, Member 1 (SMARCB1) as a recurrent feature of RMC. SMARCB1 is a core subunit of the switch/sucrose nonfermenting (SWI/SNF) complex, which is involved in adenosine triphosphate-dependent chromatin remodeling, and has been implicated in the development of rare pediatric tumors, among other malignancies.[6] Because of the lack of effective therapies and poor prognosis of RMC patients, further investigation into the mechanism of loss of SMARCB1, as well as identification of other genetic alterations, might be important for novel therapeutic strategies.

In this study, we retrospectively identified all cases of RMC diagnosed at our center from 1995 to 2015. The objective was to report on clinical outcomes to systemic therapy and characterize the genomic features of these tumors.

Patients and Methods

Study Population

Before a retrospective review of patients with RMC, the Memorial Sloan Kettering Cancer Center (MSKCC) institutional review board approved this study. Patients were identified from an institutional database that includes all pathology reports from 1993 to present, with data cutoff of September 25, 2015. Patients were included if the pathology report documented RMC. Electronic medical records were then queried for clinical data.

Response to Therapy

Imaging studies were performed per standard of care at MSKCC, and consisted of computed tomography (CT) imaging of the chest, abdomen and pelvis, or chest x-ray and abdominal magnetic resonance imaging if CT was not available. All imaging for this study was reviewed by a radiologist (J.C.) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines.[7] Patients who had pre- as well as post-therapy imaging, and received at least 1 cycle or month of therapy, were evaluable for response according to RECIST. Patients were considered to have progression of disease if there was either progression according to RECIST criteria or if they discontinued therapy because of worsening symptoms or decline in performance status.

Data Analysis

Baseline characteristics and treatment received were summarized descriptively. OS was calculated using Kaplan–Meier estimates from the date of initial oncology visit until death, and patients who were still alive at the data cutoff were censored at date of last follow-up. Progression-free survival (PFS) was calculated using Kaplan–Meier estimates from initiation of systemic therapy until date of radiographic or clinical progression, or death, whichever was first.

Immunohistochemical Analysis

Patients who had signed consent for specimen research use and who had available formalin-fixed, paraffin-embedded (FFPE) tissue were further evaluated. All samples were again reviewed by a genitourinary pathologist (Y.-B.C.) to confirm diagnosis, and to select for areas of maximum tumor content for DNA extraction. Immunohistochemistry for SMARCB1 was performed in 5-μm FFPE tissue sections using an automated Ventana Benchmark system (Ventana Medical Systems) and a mouse monoclonal antibody (1:100, BAF47; BD Bioscience).

Fluorescence In Situ Hybridization Analysis

Fluorescence in situ hybridization (FISH) analysis was performed on paraffin sections using a 3-color probe mix comprising bacterial artificial chromosome clones for *5′SMARCB1* (RP11-248J22, RP11-1112A23; labeled with Red deoxyuridine triphosphate [dUTP]), *SMARCB1* (RP11-71G19; labeled Orange with dUTP) and *3′SMARCB1* (RP11-80O7, RP11-76E8; labeled Green with dUTP). Probe labeling, hybridization, posthybridization washing, and fluorescence detection were performed according to standard laboratory procedures. Slides were scanned using a Zeiss Axioplan 2i epifluorescence microscope equipped with a megapixel charged-coupled device camera (CV-M4^{+}CL, JAI) controlled by Isis 5.5.9 imaging software (MetaSystems Group Inc, Waltham, MA). Signal counts were performed on captured images with a minimum of 50 discrete tumor nuclei scored.

Genomic Analysis

If patients had blood samples available, these were used for DNA extraction for matched normal control. Genomic alterations in key cancer-associated genes were identified using exome capture using hybridization followed by next-generation sequencing (NGS) using the Integrated Mutation Profiling of Actionable Cancer Targets assay, which included 341 cancer-related genes in an earlier iteration (n = 2), and 410 genes in the updated platform (n = 4).[8] For tumors with no matched normal controls for sequencing, common single-nucleotide polymorphisms were filtered out. Because remaining rare variants could not be reliably categorized as somatic or germ line, they were all assessed for possible germ line pathogenicity according to American College of Medical Genetics (ACMG) standards.[9]

Results

Patient and Tumor Characteristics

Thirty-six patients were diagnosed with RMC from 1995 to 2015. Key patient and tumor characteristics are summarized in Table 1. The median age at diagnosis was 27.5 (range, 12-72) years, and 27 patients (75%) were male. Twenty-seven patients had hemoglobin electrophoresis results, and all showed sickle cell trait. Of the 24 patients who self-reported race, 20 (83%) were African-American. Of the 4 patients who identified as