Published in final edited form as:

Clin Genitourin Cancer. 2017 December ; 15(6): e987–e994. doi:10.1016/j.clgc.2017.04.012.

Genomic Characterization of Renal Medullary Carcinoma and Treatment Outcomes

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Abstract

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

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Conflicts of Interest:

CHL: Consulting (Exelixis); Research funds to institute (Pfizer, Eisai)

MHV: Consulting (Pfizer, Novartis, Exelixis, Calithera, Natera); Research grants (BMS, Genentech/Roche); Travel funding (Novartis and Takeda)

DRF: Consulting (Bayer and Seattle 75 Genetics); Research funding (Novartis)

RJM: Consulting (Pfizer, Novartis, Exelixis, Eisai); Research funds to institution (Pfizer, Genentech/Roche, Novartis, BMS, Eisai, Exelixis)

JJH: Honoraria (Chugai Pharmaceutical); Consulting (Novartis, Chugai Pharmaceutical, Eisai); Research funding (Novartis, Pfizer, CGI)

YK: Employed within 2 years at BioReference Laboratories

All the remaining authors have no disclosures.

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 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 Kaplan-Meier method.

Results and limitations—The median age in the cohort was 28 years (range 12–72), and all patients tested had sickle cell trait. Overall survival was 5.8 months (95% 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.

Keywords

kidney cancer; retrospective analysis; chemotherapy; genomics; 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 15–26 years.^{1–3} Most patients present with advanced disease and, despite therapy, overall survival is usually less than 1 year.

There is no defined standard treatment for this rare entity. Most patients receive platinum-based therapy based on 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 found that only a minority of patients respond to chemotherapy.⁴ Targeted therapy with vascular endothelial growth factor (VEGF)-inhibitors or mTOR inhibitors have also been used with disappointing results.⁵

Given the aggressive nature and poor outcomes of this disease, there is great need to identify novel molecular therapeutic targets. Several studies have found loss of expression of SMARCB1 as a recurrent feature of RMC. SMARCB1 is a core subunit of the switch/sucrose non-fermenting (SWI/SNF) complex, which is involved in ATP-dependent chromatin remodeling, and has been implicated in the development of rare pediatric tumors, among other malignancies.⁶ Given 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, may 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.

Methods

Study Population

Prior to 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 cut-off on 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) of the chest, abdomen and pelvis, or chest x-ray and abdominal MRI 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 both pre-and post-therapy imaging, and received at least one cycle or month of therapy, were evaluable for response by RECIST. Patients were considered to have progression of disease if there was either progression by RECIST criteria or if they discontinued therapy due to worsening symptoms or decline in performance status.

Data Analysis

Baseline characteristics and treatment received were summarized descriptively. Overall survival (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 cut-off 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 automated Ventana Benchmark system (Ventana Medical Systems) and a mouse monoclonal antibody (1:100, BAF47, BD Bioscience).

Fluorescence in situ hybridization (FISH) Analysis

FISH analysis was performed on paraffin sections using a 3-color probe mix comprising BAC clones for 5' *SMARCB1* (RP11-248J22, RP11-1112A23; labeled with Red dUTP), *SMARCB1* (RP11-71G19; labeled Orange with dUTP) and 3' *SMARCB1* (RP11-80O7, RP11-76E8; labeled Green with dUTP). Probe labeling, hybridization, post-hybridization 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 CCD 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 by hybridization followed by next-generation sequencing (NGS) under the IMPACT (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 who did not have matched normal controls for sequencing, common single-nucleotide polymorphisms were filtered out. Since remaining rare variants could not be reliably categorized as somatic or germline, they were all assessed for possible germline pathogenicity according to 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 years (range 12–72), 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 Caucasian, 2 had sickle cell trait and 2 had unknown sickle cell status. Most patients were symptomatic at presentation, with only one patient whose tumor was found incidentally, and the median maximum tumor dimension was 5.9cm (range 2.5–14.2cm). Most tumors were right sided (67%). Of the 33 patients whose staging was known at diagnosis, 27 (75%) presented with metastatic disease at diagnosis. Of the 6 patients who initially presented with localized disease, all but 1 had disease recurrence at time of last follow-up. The most common sites of metastases were lymph nodes (86%), lung (81%), bone (44%) soft tissue (39%), and liver (36%). Two patients had documented brain metastases.

Survival Outcome and Treatment Response

With a median follow-up of 5.1 months, overall survival (OS) in the 32 evaluable patients was 5.8 months (95% CI 4.1–10.9) (Fig. 1). Eighteen patients received first-line therapy at our institution, 11 second-line, and 3 third-line or more. Most patients received a platinum combination (n=12), either as first or second-line therapy. Of these patients, 11 had

radiographic or clinical progression at time of analysis, with a median PFS of 2.5 months (95% CI 1.2-not reached) (Fig. 2); 10 were evaluable by RECIST v1.1 criteria: 4 patients had a partial response, 2 had stable disease, 4 had progressive disease (Table 2). Platinum combination therapies used included: carboplatin and gemcitabine (n=6), cisplatin and gemcitabine (n=3), cisplatin and paclitaxel (n=1), carboplatin and paclitaxel (n=1), and carboplatin/gemcitabine/paclitaxel (n=1). Five patients received mTOR inhibitors or vascular endothelial growth factor (VEGF)-targeted therapy. Therapies used included everolimus plus bevacizumab as part of a clinical trial (n=2), sunitinib (n=2), and temsirolimus (n=1); no patients had objective responses.¹⁰ Other therapies used included monotherapies with gemcitabine, pemetrexed, doxorubicin, capecitabine, none produced a durable response. One patient received methotrexate/vinblastine/doxorubicin/cisplatin (MVAC) and another paclitaxel/ifosfamide/cisplatin (TIP) after progressing on carboplatin/gemcitabine; neither had a durable response. Of note, one patient received bortezomib and had a complete response; this case has been previously published.¹¹ The patient was lost to follow-up after 72 months and tumor molecular analysis was not performed.

Molecular Characteristics

Twenty-three patients had tumor tissue available for staining for SMARCB1 (INI1) expression, and all had loss of SMARCB1. Ten patients had sufficient tissue for fluorescent *in situ* hybridization (FISH) analysis for *SMARCB1* (Table 3). FISH analysis revealed loss of heterozygosity with concurrent translocation in 8 patients, and biallelic loss of *SMARCB1* in 2 patients. Six patients had tissue available for NGS (Table 3), with 3 run with matched normal and 3 run without matched normal. No mutations of *SMARCB1* were identified through NGS. The only recurrently altered genes were *POLE* and *MTOR* in samples without a matched germline control for filtering; based on allele frequency and ACMG criteria, these variants were thought to be probably germline “variants of unknown significance” (Supplementary Table 1).

Discussion

RMC is a rare subtype of renal cell carcinoma with an aggressive clinical course, historically grouped with other distal nephron tumors such as collecting duct carcinoma. There has been debate, however, on whether these neoplasms are within a spectrum or whether they are two separate entities.^{12, 13} For example, RMC has distinct clinical features—compared to collecting duct carcinoma, patients with RMC are younger, predominantly male and have sickle cell trait or disease.¹⁴ Our study cohort was typical of those previously reported- most patients were male (75%), presenting with metastatic disease (75%), and all patients tested had sickle cell trait. Tumors were highly aggressive, with the majority of patients developing metastases in the lymph nodes and lung, and with a poor median OS of 5.8 months.

Although there is no standard treatment for RMC, given similar pathologic features to distal nephron tumors, it has historically been treated with platinum-based regimens also commonly used in collecting duct carcinomas (CDC).¹⁵ Given the rarity of RMC, prospective treatment studies are difficult to conduct, and evidence for the effectiveness therapy is limited to case reports and small series. In this study, we analyzed responses to

platinum-based therapies in 10 patients evaluable by RECIST criteria, the largest cohort with therapy response published to our knowledge. Responses to platinum-based therapy were seen in 40% of patients, with an additional 20% with stable disease. However, these responses were short-lived, with a median PFS of 2.5 months. Furthermore, no patients had a response to mTOR inhibitors or VEGF-targeted therapies.

New therapies are clearly needed in this disease. We sought to investigate unique molecular markers that could become the target of novel therapies. Pathologically, a consistent finding in RMC has been the loss of staining for SMARCB1.² SMARCB1 is a component of the chromatin remodelling complex SWI/SNF and acts as a tumor suppressor, with germline heterozygous loss leading to a rhabdoid predisposition syndrome.¹⁶ Previous studies characterizing the mechanism of loss of *SMARCB1* have shown that RMC tumors often harbor somatic mutations or monoallelic loss of *SMARCB1*.¹⁷ In the study cohort, all patients had loss of *SMARCB1*, either through hemizygous deletions and additional translocation in the remaining allele, or biallelic deletions. By comparison, in collecting duct carcinoma, which is morphologically similar to RMC, only infrequent truncating mutations in *SMARCB1* have been seen (18% of tumors in a series).¹⁸ Next-generation sequencing revealed no additional recurrent mutations in matched tumor and normal samples. This finding is in concordance with a previously published report of 5 cases of RMC, in which 4 tumors harbored translocations, and a fifth tumor showed biallelic loss.¹⁹ Although we did not perform further analysis to identify the translocation partner, in that study, four different translocation partners were identified. Together, this suggests that these genetic alterations in *SMARCB1* induce loss of function as opposed to a *de novo* function. Additional studies would be necessary to determine whether loss of *SMARCB1* is necessary and sufficient for tumorigenesis and how sickle cell trait contributes to pathogenesis.

Biallelic loss of *SMARCB1* is found in other aggressive neoplasms including malignant rhabdoid tumors, atypical teratoid/rhabdoid tumors, and epithelioid sarcomas.¹⁶ Unlike rhabdoid tumors, which mostly harbor *SMARCB1* deletions or mutations, it appears that in RMC, *SMARCB1* alterations are mostly hemizygous deletions with concurrent translocations or homozygous deletions.^{20, 21}

There has been recent interest in targeting EZH2 (Enhancer of Zeste homolog 2) in SMARCB1 deficient tumors. EZH2 is the catalytic subunit of the polycomb repressive complex 2 (PRC2), which catalyzes methylation of specific lysine residues of histone H3, and aberrant EZH2 methylation has been associated with malignancy.^{22, 23} SWI/SNF and PRC2 have antagonistic functions and loss of SMARCB1 function leads to overactivation of PRC2.²⁴ This has led investigators to test EZH2 inhibitors in SMARCB1 deficient tumors. Preclinical data in SMARCB1 deficient cell lines has shown EZH2 inhibitors can lead to apoptosis and differentiation.^{25, 26} There is an ongoing Phase II trial of the EZH2 inhibitor tazemetostat in SMARCB1 deficient tumors. This study confirms that RMC appears uniformly deficient in SMARCB1 through biallelic inactivation, and should be considered a candidate for testing EZH2 inhibitor therapy.

This study is limited by several factors. First, treatment responses were assessed in a retrospective fashion, although the radiologist was blinded to treatment received. The small

number of tumors available for sequencing limits definite conclusions on other recurrently altered genes. Nevertheless, despite these limitations, this study shows that RMC is molecularly distinct from other renal tumors and characterized by *SMARCB1* translocations and deletions, and that platinum-based chemotherapy has activity in this disease.

Conclusions

These findings show that RMC is an aggressive malignancy that can respond to platinum-based chemotherapy, however, responses are short-lived and overall survival remains poor. RMC is characterized by deletions and translocations of *SMARCB1*, which codes for a protein in the SWI/SNF chromatin remodeling complex. Mutations in the SWI/SNF complex are poorly understood, and more research is needed to understand the role of *SMARCB1* in the pathogenicity of renal medullary carcinoma and potential targeted therapies. Clinical trials are difficult to conduct in rare diseases, making translational work an important way to uncover potential therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge the members of the Molecular Diagnostics Service in the Department of Pathology.

Funding Sources: This work was supported by the Marie-Josée and Henry R. Kravis Center for Molecular Oncology and National Institutes of Health/National Cancer Institute Cancer Center Support [Grant P30 CA008748], the Randall MacDonald Kidney Cancer Research Fund, The Robert and Kate Niehaus Center for Inherited Cancer Genomics at MSKCC, the T32 “T32-CA009207 from the National Institutes of Health,” Cycle for Survival and The Society of Sloan Kettering Research Grant

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Clinical Practice Points

- Renal medullary carcinoma is a rare and aggressive type of kidney cancer usually treated with platinum-based therapy based on experience with urothelial carcinoma and limited case series.
- 40% of patients had a partial response to platinum-based therapy, but these responses were short-lived, and there were no responses to targeted anti-VEGF or mTOR therapies.
- Fluorescence *in situ* hybridization for SMARCB1 showed loss of heterozygosity with concurrent translocation in most tumors, and biallelic loss in the remaining.
- Given the poor outcomes with conventional therapy, research should go into targeting the SMARCB1 pathway.

Fig. 1.
Kaplan-Meier overall survival

Fig. 2.
Progression free survival from initiation of platinum based chemotherapy

Table 1

Patient and Tumor Characteristics

Age at diagnosis	27.5 (12 – 72)
Sex	
Male	27 (75%)
Female	9 (25%)
Race/Ethnicity	
African American/Black	20 (56%)
White	4 (11%)
Unknown	12 (33%)
Sickle Cell Trait	
Yes	27 (75%)
Unknown	9 (25%)
KPS	
80	18 (50)
<80	14 (39)
Unknown	4 (11)
Nephrectomy	
Yes	18 (50%)
No	18 (50%)
Kidney involved	
Right	24 (67%)
Left	11 (30 %)
Both	1 (3%)
Maximum Primary Tumor Dimensions	5.9 (2.5 – 14.2cm)
<4	3 (8%)
4 – 7	17 (47%)
>7	7 (20 %)
Unable to be determined	9 (25%)
Stage at Diagnosis	
I	1 (3%)
II	0
III	5 (14%)
IV	27 (75%)
Unknown	3 (8%)
Symptoms at Diagnosis	
Flank Pain	18 (50%)
Hematuria	12 (33%)
Pulmonary	7 (19%)
Systemic	7 (19%)

Age at diagnosis	27.5 (12 – 72)
Incidental imaging	1 (3%)
Other	5 (14%)
Location of Metastases	
Lymph Nodes	31 (86%)
Lung	29 (81%)
Bone	16 (44%)
Soft tissue	14 (39%)
Liver	13 (36%)
Adrenal	6 (17%)
Brain	2 (6%)

KPS=Karnofsky Performance Score

Table 2**Radiographic**

Response to Platinum-based Therapy and Progression Free Survival (PFS)

Patient	First Platinum-Based Therapy	Line of Therapy	Best Response ^a	PFS (months)
1	Carboplatin/gemcitabine	First	PR	4.9
2	Carboplatin/gemcitabine	First	PR	3.9+
3	Carboplatin/gemcitabine	First	PD	2.0
4	Carboplatin/gemcitabine	First	SD	1.2
5	Carboplatin/gemcitabine	First	NE	2.9
6	Carboplatin/gemcitabine	First	NE	0.1
7	Cisplatin/gemcitabine	First	PD	2.0
8	Cisplatin/gemcitabine	First	PD	0.7
9	Cisplatin/gemcitabine	First	PR	5.4
10	Cisplatin/paclitaxel	First	PD	1.1
11	Carboplatin/gemcitabine/paclitaxel	Second	PR	7.0
12	Carboplatin/paclitaxel	Second	SD	3.1

PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable

^aResponse assessed by RECIST v1.1 criteria

Immunohistochemistry of SMARCB1 protein, results of fluorescence *in situ* hybridization of SMARCB1, and tumor targeted next-generation sequencing

Table 3

Tumor	Tissue Source	SMARCB1 loss by IHC	SMARCB1 Alterations by FISH	Gene Mutations ^a	Protein change
1 ^b	Met	Yes	Translocation / Hemizygous Loss	<i>ERG</i>	p.R302C
2	Met	Yes	Translocation / Hemizygous Loss	Not performed	
3	Met	Yes	Translocation / Hemizygous Loss	Not performed	
4	Met	Yes	Homozygous loss	<i>MTOR</i>	p.L172fs
				<i>POLE</i>	p.F815S
				<i>SETD2</i>	p.R2024X
				<i>R4SA1</i>	p.N1038fs
				<i>AR</i>	p.457_461del
				<i>ATRX</i>	p.S598P
5 ^b	Right kidney	Yes	Translocation / Hemizygous Loss	<i>PDGFRB</i>	p.G239R
6	Met	Yes	Translocation / Hemizygous Loss	Not performed	
7 ^b	Met	Yes	Translocation / Hemizygous Loss	<i>NF1</i>	p.L1339F
				<i>NSD1</i>	p.E2550fs
8	Right kidney	Yes	Translocation / Hemizygous Loss	Not performed	
9	Right kidney	Yes	Homozygous loss	<i>TET1</i>	p.L120R
				<i>MTOR</i>	p.V1181A
				<i>SPEN</i>	p.R773K
				<i>GPS2</i>	p.R323Q
				<i>AKT3</i>	p.Y452C
				<i>POLE</i>	p.A186T
				<i>KMT2A</i>	p.E659K
				<i>ERBB2</i>	p.A1212G
10	Met	Yes	Translocation / Hemizygous Loss	<i>POLE</i>	p.I1982V
				<i>SOC1</i>	p.V45_P46dup
				<i>SOX9</i>	p.Q439Hfs*135

IHC = immunohistochemistry; FISH = fluorescence *in situ* hybridization; deep del = deep deletion; amp = amplification; met = metastasis
Mutations include missense, nonsense, frameshift, and deletions
Matched tumors were sequenced with normal blood in parallel to facilitate somatic calling

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