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European Association of Urology

Platinum Priority – Kidney Cancer
Editorial by XXX on pp. x–y of this issue

Genomic Biomarkers of a Randomized Trial Comparing First-line Everolimus and Sunitinib in Patients with Metastatic Renal Cell Carcinoma

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Article info

Article history:
Accepted October 5, 2016

Associate Editor:
Stephen Boorjian

Keywords:
Genomic biomarker
Kidney cancer
Targeted therapy
Everolimus
Sunitinib
Tumor suppressor gene
PBRM1
SETD2
BAP1
KDM5C

Abstract

Background: Metastatic renal cell carcinoma (RCC) patients are commonly treated with vascular endothelial growth factor (VEGF) inhibitors or mammalian target of rapamycin inhibitors. Correlations between somatic mutations and first-line targeted therapy outcomes have not been reported on a randomized trial.
Objective: To evaluate the relationship between tumor mutations and treatment outcomes in RECORD-3, a randomized trial comparing first-line everolimus (mTOR inhibitor) followed by sunitinib (VEGF inhibitor) at progression with the opposite sequence in 471 metastatic RCC patients.
Design, setting, and participants: Targeted sequencing of 341 cancer genes at ~540× coverage was performed on available tumor samples from 258 patients; 220 with clear cell histology (ccRCC).
Outcome measurements and statistical analysis: Associations between somatic mutations and median first-line progression free survival (PFS1L) and overall survival were determined in metastatic ccRCC using Cox proportional hazards models and log-rank tests.
Results and limitations: Prevalent mutations (≥ 10%) were *VHL* (75%), *PBRM1* (46%), *SETD2* (30%), *BAP1* (19%), *KDM5C* (15%), and *PTEN* (12%). With first-line everolimus, *PBRM1* and *BAP1* mutations were associated with longer (median [95% confidence interval {CI}] 12.8 [8.1, 18.4] vs 5.5 [3.1, 8.4] mo) and shorter (median [95% CI] 4.9 [2.9, 8.1] vs 10.5 [7.3, 12.9] mo) PFS1L, respectively. With first-line sunitinib, *KDM5C* mutations were associated with longer PFS1L (median [95% CI] of 20.6 [12.4, 27.3] vs 8.3 [7.8, 11.0] mo). Molecular subgroups of metastatic ccRCC based on *PBRM1*, *BAP1*, and *KDM5C* mutations could have predictive values for patients treated with VEGF or mTOR inhibitors. Most tumor DNA was obtained from primary nephrectomy samples (94%), which could impact correlation statistics.
Conclusions: *PBRM1*, *BAP1*, and *KDM5C* mutations impact outcomes of targeted therapies in metastatic ccRCC patients.

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http://dx.doi.org/10.1016/j.eururo.2016.10.007

Please cite this article in press as: Hsieh JJ, et al. Genomic Biomarkers of a Randomized Trial Comparing First-line Everolimus and Sunitinib in Patients with Metastatic Renal Cell Carcinoma. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.10.007

Patient summary: Large-scale genomic kidney cancer studies reported novel mutations and heterogeneous features among individual tumors, which could contribute to varied clinical outcomes. We demonstrated correlations between somatic mutations and treatment outcomes in clear cell renal cell carcinoma, supporting the value of genomic classification in prospective studies.

1. Introduction

Clear cell renal cell carcinoma (ccRCC) is most common histological subtype and accounts for the most RCC-specific deaths. The genetic inactivation of *Von Hippel Lindau* (*VHL*) tumor suppressor gene was the only known prevalent oncogenic driver event in ccRCC for decades [1]. Recent analyses of ccRCC using next-generation sequencing (NGS) revealed novel, common mutations including *PBRM1*, *BAP1*, *SETD2*, and *KDM5C* [2]. These genes encode proteins that regulate chromatin [3] and most reported somatic mutations result in loss of function, indicating that these proteins function as tumor suppressors. Thus far, analyses of published cohorts encompassing Stages I–IV kidney cancer patients have suggested prognostic values of individual mutations [4,5]. However, large-scale mutation profiles of Stage IV kidney cancer are lacking.

Inhibitors of vascular endothelial growth factor (VEGF) or mammalian target of rapamycin (mTOR) signaling pathways are standard treatment options for patients with metastatic RCC (mRCC) [6]. RECORD-3 (Renal Cell Cancer Treatment With Oral RAD001 Given Daily) was a randomized phase 2 trial comparing sunitinib, a VEGF receptor-tyrosine kinase inhibitor, with everolimus, an mTOR inhibitor, in previously untreated patients with mRCC (N = 471) [7]. After disease progression, patients crossed over to the alternative agent for second-line therapy. Most enrolled patients (~85%) had metastatic ccRCC. Median first-line progression-free survival (PFS1L; 7.9 mo, everolimus; 10.7 mo, sunitinib; hazard ratio [HR]: 1.4; 95% confidence interval [CI]: 1.2, 1.8) and final median overall survival (OS; 22.4 mo, everolimus-sunitinib; 29.5 mo, sunitinib-everolimus; $HR_{EVE\text{-}SUN/SUN\text{-}EVE}$: 1.1; 95% CI: 0.9, 1.4) [7,8] favored the standard sequence of sunitinib followed by everolimus [6,9]. Case studies involving cancer gene mutations of advanced (Stage IV or recurrent metastatic) ccRCC have indicated a potential correlation between mutations and treatment response to targeted therapy [10–12]; however, these associations have not been evaluated in a large clinical trial setting.

To address these questions, we leveraged archived tumor samples collected from the RECORD-3 study, sequenced 341 cancer genes, and performed correlation analysis.

2. Materials and methods

2.1. Patients, study design, and treatment

The RECORD-3 trial design has been previously reported [7]. Patients received everolimus 10 mg/d or sunitinib 50 mg/d in a crossover design. Patients were randomly assigned 1:1 to sequentially receive either everolimus-sunitinib (n = 238) or sunitinib-everolimus (n = 233), and stratified by Memorial Sloan-Kettering Cancer Center (MSKCC) risk criteria [13]. Adult patients with measurable mRCC of any histology who had not previously received systemic therapy, and with a Karnofsky performance status ≥70% were included. All patients gave informed consent.

2.2. Tumor DNA and MSK-Integrated Mutation Profiling of Actionable Cancer Targets

Hematoxylin and eosin slides of available tumor tissue from RECORD-3 were reviewed by a dedicated genitourinary pathologist (YC). Unstained sections were microdissected to ensure tumor purity. DNA was purified using the DNeasy Blood and Tissue Kit and subjected to ultra-deep sequencing using the MSK-Integrated Mutation Profiling of Actionable Cancer Targets platform [14].

2.3. Statistical analysis

Associations between PFS1L (and OS), first-line treatment (treatment regimen), and gene alteration status (mutant type [MT] or wild type [WT]) were investigated. All nonsynonymous mutations were considered while defining the alteration status. Median PFS1L (and OS) by first-line treatment (treatment regimen) and alteration status (MT vs WT) were determined by the Kaplan-Meier method. HR (95% CIs) are estimated from a Cox proportional hazards (PH) model for PFS1L (OS). The model included terms for mutation status, treatment arm, interaction between treatment arms and mutation status groups, with stratification by MSKCC risk groups and adjustment for baseline covariates (RCC histology when combining data from clear and nonclear cell, number of metastatic sites, baseline lactate dehydrogenase levels). Differences between survival curves of PFS1L (and OS) for each mutation status group and treatment arm were tested using the log-rank test. All p values were not adjusted for multiple testing. When exploring associations with OS, all ccRCC patients with NGS data were included based on the randomized treatment regimen, regardless of their crossover status, and no adjustments were performed for confounding effects of crossover. Patterns of mutual exclusivity or co-occurrence were explored via odds ratio, and statistical significance for the relationship between gene pairs was assessed using Fisher exact test [15].

3. Results

3.1. Study cohort

Among 258 successfully sequenced tumors, 220 were of clear cell histology (first-line everolimus, n = 109; first-line sunitinib, n = 111; Fig. 1). For a clear correlation analysis, we only included ccRCC patients. Our NGS ccRCC cohort (n = 220) reflects patient characteristics of the original 471 patients included in RECORD-3 (Table 1). Patient characteristics of the total biomarkers population (ccRCC and non-ccRCC) are shown (Supplementary Table 1).

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