Original Study

Is Late Recurrence a Predictive Clinical Marker for Better Sunitinib Response in Metastatic Renal Cell Carcinoma Patients?

Oktay Bozkurt,[1] Ilhan Hacıbekiroglu,[2] Muhammet Ali Kaplan,[3] Yakup Duzkopru,[4] Mukremin Uysal,[5] Halit Karaca,[1] Veli Berk,[6] Mevlude Inanc,[6] Ayse Ocak Duran,[1] Ersin Ozaslan,[1] Mahmut Ucar,[1] Metin Ozkan[1]

Abstract

Although there has been an increase in overall and progression-free survival with the use of novel targeted therapies in metastatic renal cell carcinoma (mRCC) in recent times, predictive markers to determine which patients would benefit from tyrosine kinase inhibitor therapies are needed. The late recurrence might be a predictive marker for response to sunitinib treatment in patients with mRCC.

Background: We investigated the clinicopathological features in patients with recurrent renal cell carcinoma (RCC) within 5 years or more than 5 years after nephrectomy and determined predictors of overall survival (OS) and progression-free survival (PFS) after disease recurrence in the administration of first-line sunitinib in the treatment of metastatic RCC (mRCC). **Patients and Methods:** In this study we enrolled 86 Turkish patients with mRCC who received sunitinib. Univariate analyses were performed using the log rank test. **Results:** Fifty-six patients (65%) were diagnosed with disease recurrence within 5 years after radical nephrectomy (early recurrence) and 30 patients (35%) were diagnosed with recurrence more than 5 years after radical nephrectomy (late recurrence). Fuhrman grade was statistically significantly different between the 2 groups ($P = .013$). The late recurrence patients were significantly associated with the Memorial Sloan Kettering Cancer Center favorable risk group compared with patients with early recurrence ($P = .001$). There was a statistically significant correlation between recurrence time and the rate of objective remission (ORR) (the late recurrence group vs. the early recurrence group: 43.3% vs. 14.3%, respectively; $P = .004$). From the time of disease recurrence, the median OS was 42.0 (95% confidence interval [CI], 24.4-59.5) months in the late recurrence group, and 16 (95% CI, 11.5-20.4) months in the early recurrence group ($P = .001$). Median PFS was 8 (95% CI, 4.05-11.9) months in the early recurrence group, and 20 (95% CI, 14.8-25.1) months in the late recurrence group ($P \leq .001$). **Conclusion:** The study demonstrated a potential prognostic value of late recurrence in terms of PFS, OS, and ORR.

Clinical Genitourinary Cancer, Vol. 13, No. 6, 548-54
Keywords: Late recurrence, Prognostic factor, Renal cell carcinoma, Sunitinib, Survival

Introduction

Renal cell carcinoma (RCC) is the third most frequent malignancy of the urinary tract and comprises approximately 3% of all adult malignancies.[1] Prognosis in patients with untreated metastatic renal cell disease remains poor and 5-year life expectancy is <10%.[2] Metastatic RCC (mRCC) has a poor response to conventional chemotherapy and radiotherapy. Immunotherapy such as with the cytokines interleukin-2 and interferon (IFN)-α is associated with modest response rates of <20% and significant toxicities.[3,4] The treatment of RCC has changed dramatically in recent times because

[1]Department of Medical Oncology, Erciyes University Faculty of Medicine, Kayseri, Turkey
[2]Department of Medical Oncology, Trakya University Faculty of Medicine, Edirne, Turkey
[3]Department of Medical Oncology, Dicle University Faculty of Medicine, Diyarbakır, Turkey
[4]Department of Internal Medicine, Dicle University Faculty of Medicine, Diyarbakır, Turkey
[5]Department of Medical Oncology, Afyon Kocatepe University Faculty of Medicine, Afyon, Turkey
[6]Kayseri Training and Research Hospital Medical Oncology Department, Kayseri, Turkey

Submitted: May 6, 2015; Revised: Jul 14, 2015; Accepted: Jul 18, 2015; Epub: August 3, 2015

Address for correspondence: Oktay Bozkurt, MD, Department of Medical Oncology, Erciyes University, School of Medicine, M.K. Dedeman Oncology Hospital, 38035 Kayseri, Turkey
Fax: +90-352-4378659; e-mail contact: bozkurt.oktay8@gmail.com

1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2015.07.005

of an improved understanding of the underlying molecular pathways and especially the role of angiogenesis in RCC.

Sunitinib (Sutent; Pfizer) is an orally administered inhibitor of the split kinase domain family of receptor tyrosine kinases (including vascular endothelial growth factor [VEGF] receptor types 1-3, platelet-derived growth factor receptor [PDGFR]-α, and PDGFR-β).[5] Its antitumor activity results from the inhibition of angiogenesis via blockade of the endothelial cell VEGF pathway and PDGFR-β expression in pericytes but also tumor cell proliferation.[6] Sunitinib has recently been established as first-line treatment for treatment-naive patients with mRCC, according to the results of a randomized phase III trial, which showed a superior efficacy compared with IFN-α in terms of progression-free survival (PFS), objective response rate, and overall survival (OS).[7] Despite this undoubted benefit, the prognosis of metastatic kidney cancer remains poor, and the toxicity of sunitinib is substantial.[8] Therefore, identification of patients who would benefit from this treatment is important.

The Memorial Sloan Kettering Cancer Center (MSKCC) risk stratification has been improved to predict outcomes in patients with mRCC, and has been modified for trials of targeted therapy.[9] In addition to its use for estimating survival, it provides relevant clinical information to patients who receive therapy. For example, multitargeted tyrosine kinase inhibitors (TKIs) such as sunitinib or bevacizumab with interferon (IFN)-α have been cited as the preferred treatment options for mRCC patients with favorable- or intermediate-risk features.[10] In contrast, mammalian target of rapamycin (mTOR) inhibitors such as temsirolimus are proposed as a preferential treatment option for RCC patients with poor-risk features.[11] In the present study, we investigated the clinicopathological features in patients with recurrent RCC within 5 years or more than 5 years after nephrectomy and determined predictors of OS and PFS after recurrence in the administration of first-line sunitinib in mRCC.

Patients and Methods

We retrospectively evaluated 86 patients who were diagnosed with disease recurrence within 5 years and more than 5 years after radical nephrectomy due to localized RCC from January 1996 to January 2014. These patients were treated with sunitinib in February 2008 and June 2014 in a multicenter study. The study protocol was approved by the medical ethics committees of all participating centers, and all patients provided written informed consent before participating in October 2014. The study met the requirements of the Declaration of Helsinki. Demographic and clinicopathologic data such as age, sex, laboratory findings, RCC histologic subtype, Eastern Cooperative Oncology Group (EGOG) performance status (PS), areas of metastasis, and patient survival were obtained from chart reviews of RCC patients in 4 oncology departments in Turkey.

Inclusion criteria for this study were as follows: histologically confirmed recurrent RCC; at least 1 measurable lesion according to the Response Evaluation Criteria in Solid Tumors; 18 years of age or older; all patients who underwent radical or partial nephrectomy for unilateral localized RCC; previous first-line or adjuvant treatment was not administered. Patients with an EGOG PS of 4 and those with severe concomitant medical illnesses were excluded. Preoperatively all cases were staged properly with abdominal computerized tomography, chest imaging, a serum exhaustive metabolic panel and bone or brain imaging as indicated by laboratory values or symptoms. The pathologic stage was determined by the American Joint Committee on Cancer tumor, node, metastases staging system. Tumor cell differentiation was determined according to the Fuhrman grading system. Follow-up evaluation consisted of history and physical examination, routine blood tests with serum metabolic panels, and imaging every 3 to 6 months during the first 2 years, every 6 months from the third to the fifth year, and annually thereafter. Additional imaging examinations were conducted when the patient presented with symptoms related to cancer recurrence. The sites and number of recurrences were determined according to radiological findings of disease on computed tomography (CT), ultrasound, positron emission tomography (PET), and PET/CT or bone scan. Disease recurrence was described as radiographic evidence; imaging findings suspected to show disease recurrence were followed by biopsy of the doubted lesion and classified as disease recurrence after pathological confirmation.

All patients received sunitinib as first-line systemic treatment on an outpatient basis. Sunitinib was administered at the approved dose of 50 mg daily on a 4 weeks on-2 weeks off schedule. Treatment was interrupted in case of Grade 3 or 4 toxicity and was reintroduced when toxicity was Grade $\leq$1. In case of Grade 3 nonhematological toxicity or Grade 4 hematological toxicity, there was a successive reduction at a daily dose of 37.5 mg and 25 mg. Treatment was discontinued in patients with progression or severe toxicity after dose reduction. Thyroid dysfunction and arterial hypertension were managed with appropriate medication without dose reductions. Each patient was classified according to the MSKCC risk scoring system at the beginning of the treatment period. This model includes 5 adverse predictive variables, including corrected serum calcium of >10 mg/dL, hemoglobin level less than the sex-specific lower limit of normal, serum lactate dehydrogenase (LDH) > 1.5 times the normal level, Karnofsky PS <80%, and time from initial diagnosis to systemic treatment of <12 months. Each patient was then categorized into the favorable (0 points), intermediate (1 or 2 points), or poor (3 or 4 points) risk group. Tumor evaluation was performed after every 2 to 3 cycles of treatment unless clinically indicated.

Statistical Analysis

For statistical analyses of the study data, SPSS version 18.0 software was used (IBM). Associations between time to recurrence ($\geq$5 years vs. <5 years), and categorical data were evaluated using the Fisher exact test. Survival analysis was performed using the Kaplan–Meier method, and the differences among the groups were determined using the log rank test. Survival was defined as time from disease recurrence to death or last follow-up. Each variable was investigated using univariate analysis for OS predictors. Multivariate analysis was not performed because of the limited sample size and the low number of outcome events. All P values represent 2-sided tests of statistical significance, with $P < .05$ being considered statistically significant.

Results

The median patient age was 60 years (range, 24-83 years), and the 86 patients included 63 men (73.3%) and 23 women (26.7%). The