Original Study

Metformin Use and Outcome of Sunitinib Treatment in Patients With Diabetes and Metastatic Renal Cell Carcinoma

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Abstract

We analyzed the effect of metformin use on sunitinib treatment outcome in diabetic patients with metastatic renal cell carcinoma. In metformin users versus nonusers, clinical benefit was 96% versus 84% ($P = .054$), median progression-free survival was 15 versus 11.5 months ($P = .1$), and median overall survival (OS) was 32 versus 21 months ($P = .001$). In multivariate analyses of the entire patient cohort, metformin use was associated with OS.

Background: Although studies in several cancer types suggest that metformin has antitumor activity, its effect on the outcome of targeted therapies in metastatic renal cell carcinoma (mRCC) is poorly defined. We aimed to analyze the effect of metformin use on the outcome of sunitinib treatment in diabetic patients with mRCC. **Patients and Methods:** We performed a retrospective study of diabetic patients with mRCC, who were treated with sunitinib in 8 centers across 2 countries. Patients were divided into metformin users and nonusers. The effect of metformin use on response rate, progression-free survival (PFS), and overall survival (OS), was tested. Furthermore, univariate and multivariate analyses of the association between clinicopathologic factors and metformin use, and outcome were performed using the entire patient cohort. **Results:** Between 2004 and 2014, 108 diabetic patients with mRCC were treated with sunitinib. There were 52 metformin users (group 1) and 56 nonusers (group 2). The groups were balanced regarding clinicopathologic factors. Clinical benefit (partial response + stable disease) in group 1 versus 2 was 96% versus 84% ($P = .054$). Median PFS was 15 versus 11.5 months ($P = .1$). Median OS was 32 versus 21 months ($P = .001$). In multivariate analyses of the entire patient cohort (n = 108), factors associated with PFS were active smoking and pretreatment neutrophil to lymphocyte ratio > 3. Factors associated with OS were metformin use (hazard ratio, 0.21; $P < .0001$), Heng risk, active smoking, liver metastases, and pretreatment neutrophil to lymphocyte ratio > 3. **Conclusion:** Metformin might improve the OS of diabetic patients with mRCC who are treated with sunitinib.

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Introduction

Renal cell carcinoma is the most common cancer of the kidney.[1] Of patients with the disease, 20% to 30% are diagnosed with metastatic disease, and 70% to 80% of patients present with localized or locally advanced disease at diagnosis, which is potentially curable by radical surgical resection alone.[2] Among patients

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who undergo radical resection for localized disease, future metastatic disease develops in 20% to 40%.[3]

An understanding of the pathogenesis of renal cell carcinoma at the molecular level, and randomized clinical trials, have established the standard role of the orally administered vascular endothelial growth factor receptor and platelet derived growth factor receptor inhibitor sunitinib for the treatment of advanced renal cell carcinoma.[4]

The oral hypoglycemic agent metformin is widely used in the treatment of diabetes.

Data suggest that metformin might have antineoplastic properties. It might affect cancer cells indirectly by decreasing insulin levels or directly by inhibiting cancer cell proliferation and apoptosis.[5] Metformin is a potent adenosine monophosphate–activated protein kinase (AMPK) activator.[6] When activated, AMPK inactivates enzymes involved in adenosine triphosphate consumption such as fatty acid and protein synthesis.[6] Furthermore, AMPK activation inhibits the mammalian target of rapamycin (mTOR) complex 1 pathway and S6K1 phosphorylation implicated in the tumorigenesis process.[7] Metformin might also induce autophagy and apoptosis mechanisms.[8] Although some data suggest that metformin inhibits renal cell carcinoma cell proliferation in vitro,[9] its effect on the outcome of targeted therapies in metastatic renal cell carcinoma is poorly defined.

In the present study we sought to determine the effect of concomitant metformin use on the outcome of diabetic patients with metastatic renal cell carcinoma who are treated with sunitinib.

Patients and Methods

Study Group

We reviewed the records of patients (unselected cohort, international multicenter database) with evidence of metastatic renal cell carcinoma, who were treated with sunitinib, between February 1, 2004 and December 31, 2014, in 8 centers across 2 different countries: the United States (Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD) and Israel (Institutes of Oncology at Meir Medical Center, Kfar Saba; Asaf Harofe Medical Center, Zerifin; Rambam Medical Center, Haifa; Sheba Medical Center, Tel Hashomer; Soroka Medical Center, Beer-Sheva; Rabin Medical Center, Petach Tikva; Tel Aviv Sourasky Medical Center, Tel Aviv). Diabetic patients identified and comprised the study group. Patient data were retrospectively collected from electronic medical records and paper charts, including the following clinicopathologic information: age, sex, tumor histology, the time interval from initial diagnosis to sunitinib treatment initiation, Eastern Cooperative Oncology Group performance status, previous treatments for renal cell carcinoma, sites of metastases, laboratory findings, blood pressure levels during treatment, sunitinib dose reduction and/or treatment interruption, and treatment outcomes including objective response rate, progression-free survival (PFS), and overall survival (OS). Outcome data were last updated on December 31, 2014. Data on the concomitant use of medications, including angiotensin system inhibitors (angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers) and metformin, were gathered from patient electronic medical records and paper charts documenting baseline patient intake and regular follow-ups during treatment, pharmacy records, and by contacting patients and other treating physicians as needed. Patients were divided into 2 groups: (1) metformin users; and (2) metformin naive.

Sunitinib Treatment

All patients had objective disease progression on scans before starting sunitinib treatment. Sunitinib was prescribed as a part of standard treatment or clinical trial. It was administered orally, usually at a starting dose of 50 mg once daily, in 6-week cycles consisting of 4 weeks of treatment followed by 2 weeks without treatment, or in 3-week cycles consisting of 2 weeks of treatment followed by 1 week without treatment. In patients with significant comorbidities, treatment was initiated at a reduced dose, with subsequent dose escalation if well tolerated. Treatment dose reduction or treatment interruption were done for the management of adverse events, depending on their type and severity, according to standard guidelines. Treatment was continued until evidence of disease progression on scans, unacceptable adverse events, or death. Patient follow-up generally consisted of regular physical examinations and laboratory assessments (hematologic and serum chemical measurements), every 4 to 6 weeks, and imaging studies performed every 12 to 18 weeks.

Treatment Outcomes

Follow-up time was defined as the time from sunitinib treatment initiation to December 31, 2014. For the evaluation of response, the Response Evaluation Criteria in Solid Tumors version 1.1 was applied.[10] The response was assessed by independent radiologists and treating physicians. PFS was defined as the time from the initiation of sunitinib treatment until evidence of disease progression on scans or death from any cause. Overall survival was defined as the time from the initiation of sunitinib treatment to death from any cause.

Statistical Analysis

The group of metformin users included patients who started taking metformin before or within 1 month after beginning sunitinib treatment. To better elucidate the effect of metformin use, baseline clinical characteristics and known prognostic factors were compared between metformin users versus nonusers, to identify any potential confounding covariates. The χ^2 test was used to compare categorical end points, and 2-sample t test was used to compare continuous end points, after necessary data transformation. Baseline clinical characteristics and known prognostic factors in metastatic renal cell carcinoma treated with sunitinib[11-18] were included as confounding covariates in the analysis, including age, sex, pretreatment smoking status (active vs. past/never), histology (clear cell vs. nonclear cell), past nephrectomy, previous systemic therapies, number of metastases sites, presence of lung/liver/bone metastases, pretreatment neutrophil to lymphocyte ratio (NLR) $>$ 3, sunitinib-induced hypertension, sunitinib dose reduction or treatment interruption, mean sunitinib dose per treatment cycle, the use of angiotensin system inhibitors, and the risk according to the Heng prognostic model. Patients whose disease did not progress or who died by December 31, 2014 were censored in PFS analysis or OS analysis, respectively. PFS time and OS time were analyzed using Cox proportional hazards